09/108673
IA # 29

nucleoside, and further
comprising at least two 2'-O-methyl-ribonucleotides at each end, where the oligonucleotide
is present in intact form in the systemic plasma and in liver tissue of the mammal at least
six hours following oral administration.

L6: Entry 36 of 36
File: DWPI
Mar 16, 2000

DERWENT-ACC-NO: 1996-230367
DERWENT-WEEK: 200021

TITLE: Down-regulating gene expression in an animal - by orally administering a complementary
oligo:nucleotide with non-phospho:di:ester linkages and a 2'-substd. ribonucleotide

ABEQ:
A new method for introducing an intact oligonucleotide into a mammal comprises orally
administering an oligonucleotide of about 15 to 25 nucleotides, the oligonucleotide comprising
phosphorothioate internucleoside linkages between every nucleoside, and further comprising at
least two 2'-O-methyl-ribonucleotides at each end, where the oligonucleotide is present in intact
form in the systemic plasma and in liver tissue of the mammal at least six hours following oral
administration.

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1. Document ID: US 20010002993 A1

L10: Entry 1 of 42
File: PGPB
Jun 7, 2001

PGPUB-DOCUMENT-NUMBER: 20010002993
PGPUB-FILING-TYPE: new-utility
DOCUMENT-IDENTIFIER: US 20010002993 A1

TITLE: CONTRAST AGENTS

PUBLICATION-DATE: June 7, 2001
US-CL-CURRENT: 424/9.52

APPL-NO: 09/ 291277
DATE FILED: April 14, 1999
CONTINUED PROSECUTION APPLICATION: CPA

RELATED-US-APPL-DATA:

RLAN	RLFD	RLPC	RLKC	RLAC
09291277	Apr 14, 1999	UNKNOWN	A1	US
PCT/GB97/02898	Oct 21, 1997			US
60044452	Apr 29, 1997			

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	DOC-ID	APPL-DATE
DE	9621884.7	1996DE-9621884.7	October 21, 1996
DE	9708239.0	1997DE-9708239.0	April 23, 1997

IN: OSTENSEN, JONNY, ERIKSEN, MORTEN, FRIGSTAD, SIGMUND, RONGVED, PAL

AB: Ultrasonic visualisation of a subject, particularly of perfusion in the
myocardium and other tissues, is performed using novel gas-containing contrast agent
preparations which promote controllable and temporary growth of the gas phase in vivo
following administration and can therefore act as deposited perfusion tracers. The
preparations include a coadministerable composition comprising a diffusible component
capable of inward diffusion into the dispersed gas phase to promote temporary growth
thereof. In cardiac perfusion imaging the preparations may advantageously be coadministered
with vasodilator drugs such as adenosine in order to enhance the differences in return
signal intensity from normal and hypoperfused myocardial tissue respectively.

L10: Entry 1 of 42
File: PGPB
Jun 7, 2001

DOCUMENT-IDENTIFIER: US 20010002993 A1
TITLE: CONTRAST AGENTS

BSTX:
[0028] The composition comprising the diffusible component may take any appropriate form and may
be administered by any appropriate method, the route of administration depending in part on the
area of the subject which is to be investigated. Thus, for example, oral administration of an
appropriate composition comprising a diffusible component may be particularly useful where it is
desired to promote temporary retention of gas in the tissue of the gastrointestinal wall. In
representative embodiments of such applications the gas dispersion may be injected intravenously
in doses similar to those used in echocardiography and the diffusible component may be formulated
as an orally administrable emulsion, e.g. a perfluorocarbon-in-water emulsion as described in
further detail hereinafter, for example being used at a dose of 0.2-1.0 .mu.l perfluorocarbon/kg.
Following administration and distribution of the two compositions, growth of the gas dispersion
in the capillary blood pool in the gastric or intestinal wall may enhance contour contrast from
these regions. It will be appreciated that the reverse combination of an orally administrable gas
dispersion and intravenously injectable diffusible component may be useful in providing contour
contrast from the inner wall or mucosa of the gastrointestinal system.

BSTX:
[0074] Representative and non-limiting examples of drugs useful in accordance with this
embodiment of the invention include antineoplastic agents such as

vincristine, vinblastine,
vindesine, busulfan, chlorambucil, spiroplatin, cisplatin, carboplatin, methotrexate, adriamycin,
mitomycin, bleomycin, cytosine arabinoside, arabinosyl adenine, mercaptopurine, mitotane,
procarbazine, dactinomycin (antinomycin D), daunorubicin, doxorubicin hydrochloride, taxol,
plicamycin, aminoglutethimide, estramustine, flutamide, leuprolide, megestrol acetate, tamoxifen,
testolactone, trilostane, amsacrine (m-AMSA), asparaginase (L-asparaginase), etoposide,
interferon a-2a and 2b, blood products such as hematoporphyrins or derivatives of the foregoing;
biological response modifiers such as muramylpeptides; antifungal agents such as ketoconazole,
nystatin, griseofulvin, flucytosine, miconazole or amphotericin B; hormones or hormone analogues
such as growth hormone, melanocyte stimulating hormone, estradiol, beclomethasone dipropionate,
betamethasone, cortisone acetate, dexamethasone, flunisolide, hydrocortisone, methylprednisolone,
paramethasone acetate, prednisolone, prednisone, triamcinolone or fludrocortisone acetate;
vitamins such as cyanocobalamin or retinoids; enzymes such as alkaline phosphatase or manganese
superoxide dismutase; antiallergic agents such as amelexanox; anticoagulation agents such as
warfarin, phenprocoumon or heparin; antithrombotic agents; circulatory drugs such as propranolol;
metabolic potentiators such as glutathione; antituberculars such as p-aminosalicylic acid,
isoniazid, capreomycin sulfate, cyclosexine, ethambutol, ethionamide, pyrazinamide, rifampin or
streptomycin sulphate; antivirals such as acyclovir, amantadine, azidothymidine, ribavirin or
vidarabine; blood vessel dilating agents such as diltiazem, nifedipine, verapamil, erythritol
tetranitrate, isosorbide dinitrate, nitroglycerin or pentaerythritol tetranitrate; antibiotics
such as dapsone, chloramphenicol, neomycin, cefaclor, cefadroxil, cephalexin, cephradine,
erythromycin, clindamycin, lincomycin, amoxicillin, ampicillin, bacampicillin, carbenicillin,
dicloxacillin, cyclacillin, picloxacillin, hetacillin, methicillin, nafcillin, penicillin or
tetracycline; antiinflammatories such as diflunisal, ibuprofen, indomethacin, meclefenamate,
mefenamic acid, naproxen, phenylbutazone, piroxicam, tolmetin, aspirin or salicylates;
antiprotozoans such as chloroquine, metronidazole, quinine or meglumine antimonate;
antirheumatics such as penicillamine; narcotics such as paregoric; opiates such as codeine,
morphine or opium; cardiac glycosides such as deslaneside, digitoxin, digoxin, digitalin or
digitalis; neuromuscular blockers such as atracurium mesylate, gallamine triethiodide,
hexafluorenium bromide, metocurine iodide, pancuronium bromide, succinylcholine chloride,
tubocurarine chloride or vecuronium bromide; sedatives such as amobarbital, amobarbital sodium,
apropbarbital, butabarbital sodium, chloral hydrate, ethchlorvynol, ethinamate, flurazepam
hydrochloride, glutethimide, methotrimeprazine hydrochloride, methyprylon, midazolam
hydrochloride, paraldehyde, pentobarbital, secobarbital sodium, talbutal, temazepam or triazolam;
local anaesthetics such as bupivacaine, chloroprocaine, etidocaine, lidocaine, mepivacaine,
procaine or tetracaine; general anaesthetics such as droperidol, etomidate, fentanyl citrate with
droperidol, ketamine hydrochloride, methohexital sodium or thiopental and pharmaceutically
acceptable salts (e.g. acid addition salts such as the hydrochloride or hydrobromide or base
salts such as sodium, calcium or magnesium salts) or derivatives (e.g. acetates) thereof; and
radiochemicals, e.g. comprising beta-emitters. Of particular importance are
antithrombotic agents
such as vitamin K antagonists, heparin and agents with heparin-like activity such as antithrombin
III, dalteparin and enoxaparin; blood platelet aggregation inhibitors such as ticlopidine,
aspirin, dipyridamole, iloprost and abciximab; and thrombolytic enzymes such as streptokinase and
plasminogen activator. Other examples of therapeutics include genetic material such as nucleic
acids, RNA, and DNA of natural or synthetic origin, including recombinant RNA and DNA. DNA
encoding certain proteins may be used in the treatment of many different types of diseases. For
example, tumour necrosis factor or interleukin-2 may be provided to treat advanced cancers;
thymidine kinase may be provided to treat ovarian cancer or brain tumors; interleukin-2 may be
provided to treat neuroblastoma, malignant melanoma or kidney cancer; and interleukin-4 may be
provided to treat cancer.

2. Document ID: US 6225445 B1

L10: Entry 2 of 42

File: USPT

May 1, 2001

US-PAT-NO: 6225445
DOCUMENT-IDENTIFIER: US 6225445 B1
TITLE: Methods and compositions for lipidization of hydrophilic molecules
DATE-ISSUED: May 1, 2001

US-CL-CURRENT: 530/350; 530/380, 530/385, 530/387.1

APPL-NO: 9/ 120118
DATE FILED: July 22, 1998

PARENT-CASE:
CROSS-REFERENCE TO RELATED APPLICATIONS This application is a division of appl. Ser. No.
08/524,362, filed Sep. 5, 1995 now U.S. Pat. No. 4,907,030, which is a continuation-in-part of
appl. Ser. No. 08/349,717, filed Jan. 25, 1995, abandoned.

IN: Shen; Wei-Chiang, Ekrami; Hossein M.

AB: Fatty acid derivatives of sulfhydryl-containing compounds (for example,
sulfhydryl-containing peptides or proteins) comprising fatty acid-conjugated products with a
disulfide linkage are employed for delivery of the compounds to mammalian cells. This
modification markedly increases the absorption of the compounds by mammalian cells relative
to the rate of absorption of the unconjugated compounds, as well as prolonging blood and
tissue retention of the compounds. Moreover, the disulfide linkage in the conjugate is quite
labile in the cells and thus facilitates intracellular release of the intact compounds from
the fatty acid moieties.

L10: Entry 2 of 42

File: USPT

May 1, 2001

DOCUMENT-IDENTIFIER: US 6225445 B1

TITLE: Methods and compositions for lipidization of hydrophilic molecules

BSPR:
Alternative routes of protein and peptide delivery may include the buccal, nasal, oral,
pulmonary, rectal and ocular routes. Without exception, these routes are less effective than the
parenteral routes of administration. However, these routes of protein and peptide delivery are
still far more attractive than the parenteral routes because they offer convenience and control
to the patients. The oral route is particularly attractive because it is the most convenient and
patient-compliant.

BSPR:
Mucosal barriers, which separate the inside of the body from the outside (e.g. GI, ocular,
pulmonary, rectal and nasal mucosa), comprise a layer of tightly joined cell monolayers which
strictly regulates the transport of molecules. Individual cells in barriers are joined by tight
junctions which regulate entry into the intercellular space. Hence, the mucosa is at the first
level a physical barrier, transport through which depends on either the transcellular or the
paracellular pathways [Lee, V. H. L. (1988) CRC Critical Rev. Ther. Drug Delivery Sys. 5, 69-97].

BSPR:
In addition to providing a tight physical barrier to the transport of proteins and peptides,
mucosal barriers possess enzymes which can degrade proteins and peptides before, after, and
during their passage across the mucosa. This barrier is referred to as the enzymatic barrier. The
enzymatic barrier consists of endo- and exopeptidase enzymes which cleave proteins and peptides
at their terminals or within their structure. Enzymatic activity of several mucosa have been
studied and the results demonstrated that substantial protease activity exists in the homogenates
of buccal, nasal, rectal and vaginal mucosa of albino rabbits and that these activities are
comparable to those present in the ilium [Lee et al. (1988), supra]. Therefore, regardless of the
mucosa being considered, the enzymatic barrier present will feature strongly in the degradation
of the protein and peptide molecules.

BSPR:
In accordance with the present invention, fatty acid derivatives of sulfhydryl-containing
compounds (for example, peptides, proteins or oligonucleotides which contain or are modified to
contain sulfhydryl groups) comprising fatty acid-conjugated products with a disulfide linkage are
employed for delivery of the sulfhydryl-containing compounds to mammalian cells. This
modification markedly increases the absorption of the compounds by mammalian cells relative to
the rate of absorption of the unconjugated compounds, as well as prolonging blood and tissue
retention of the compounds. Moreover, the disulfide linkage in the conjugate is quite labile in
the cells and thus facilitates intracellular release of the intact compounds from the fatty acid
moieties. Reagents and methods for preparation of the fatty acid derivatives are also provided.

DEPR:
Pursuant to another aspect of the present invention, methods for increasing the absorption or
prolonging blood and tissue retention in a mammal of a sulfhydryl-containing compound of the
general formula PSH are provided, in which a conjugate of general formula VI is formed from the
sulfhydryl-containing compound and the conjugate is then administered to the mammal (for example,
in an aqueous solution or an oral dosage unit).

DEPR:
The fatty acid conjugates of the present invention are soluble in most buffer solutions in which
proteins and peptides are soluble. In particular, any free carboxylic acid groups are charged at
neutral pH and therefore improve the solubility of the conjugates. This greatly facilitates the
formulation of the conjugates with suitable pharmaceutically-acceptable carriers or adjuvants for
administration of the proteins or peptides to a patient by oral or other routes.

ORPL:
Smith, P. et al., "Oral absorption of peptides and proteins," Adv. Drug Delivery Rev.
8(2,3):253-290 (1992).

3. Document ID: US 6207150 B1

L10: Entry 3 of 42

File: USPT

Mar 27, 2001

US-PAT-NO: 6207150
DOCUMENT-IDENTIFIER: US 6207150 B1
TITLE: Variants of thymidine kinase, nucleic acids encoding them, and methods of using them
DATE-ISSUED: March 27, 2001

US-CL-CURRENT: 424/94.5; 435/194, 435/252.3, 435/320.1, 435/325, 435/6, 536/23.2

APPL-NO: 9/ 125099
DATE FILED: August 6, 1998

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
FR	96 01603	February 9, 1996
FR	96 09709	August 1, 1996

PCT-DATA:

APPL-NO	DATE-FILED	PUB-NO	PUB-DATE	371-DATE	102(E)-DATE
PCT/ER97/00193	January 31, 1997	WO97/29196	Aug 14, 1997	Aug 6, 1998	Aug 6, 1998

IN: Crouzet; Joel, Blanche; Francis, Couder; Michel, Cameron; Beatrice

AB: The present invention relates to a nucleic acid sequence characterized in that it is derived from the wild nucleic acid sequence coding for a thymidine kinase, said nucleic acid sequence having at least one mutation in the region corresponding to the ATP binding site and conveniently a second mutation in the N-terminal region and/or C-terminal region.

It also relates to variants of the wild thymidine kinase and their use in genic therapy.

L10: Entry 3 of 42

File: USPT

Mar 27, 2001

DOCUMENT-IDENTIFIER: US 6207150 B1

TITLE: Variants of thymidine kinase, nucleic acids encoding them, and methods of using them

BSPR:

To this end, the present invention also relates to any expression cassette comprising a nucleic acid sequence as defined above, a promoter permitting its expression and a transcription termination signal. The promoter is advantageously chosen from promoters which are functional in mammalian, preferably human, cells. More preferably, the promoter in question is one that permits the expression of a nucleic acid sequence in a hyperproliferative cell (cancer cell, restenosis, and the like). In this connection, different promoters may be used. A possible promoter is, for example, the one actually belonging to the herpes simplex type I TK gene. Sequences of different origin (responsible for the expression of other genes, or even synthetic sequences) are a, further possibility. Thus, it is possible to use any promoter or derived sequence that stimulates or represses the transcription of a gene, specifically or otherwise, inducibly or otherwise, strongly or weakly. The promoter sequences of eukaryotic or viral genes may be mentioned in particular. Possible promoter sequences are, for example, ones originating from the target cell.

Among eukaryotic promoters, it is possible to use, in particular, ubiquitous promoters (promoter of the HPRT, PGK, alpha-actin, tubulin, DHFR, and the like, genes), promoters of intermediate filaments (promoter of the GFAP, desmin, vimentin, neurofilament, keratin, and the like, genes), promoters of therapeutic genes (for example the promoter of the MDR, CFTR, factor VIII, ApoAI, and the like, genes), tissue-specific promoters (promoter of the pyruvate kinase, villin, intestinal fatty acid binding protein, smooth muscle alpha-actin, and the like, gene), promoters of specific cells of the dividing cell type, such as cancer cells, or alternatively promoters that respond to a stimulus (steroid hormone receptor, retinoic acid receptor, glucocorticoid receptor, and the like) or so-called inducible promoters. Similarly, the promoter sequences may be ones originating from the genome of a virus, such as, for example, the promoters of the adenovirus E1A and MLP genes, the CMV early promoter or alternatively the RSV LTR promoter, and the like. In addition, these promoter regions may be modified by adding activating or regulatory sequences, or sequences permitting a tissue-specific or -preponderant expression.

BSPR:

The nucleic acid sequence or vector used in the present invention may be formulated for the purpose of topical, oral, parenteral, intranasal, intravenous, intramuscular, subcutaneous, intraocular, transdermal, and the like, administration. Preferably, the nucleic acid sequence or vector is used in an injectable form. It may hence be mixed with any pharmaceutically acceptable vehicle for an injectable formulation, in particular for direct injection at the site to be treated. Possible formulations include, in particular, sterile isotonic solutions, and dry, in particular lyophilized compositions which, on addition of sterilized water or of physiological saline as appropriate, enable injectable solutions to be made up. A direct injection of the nucleic acid sequence into the patient's tumour is advantageous, since it enables the therapeutic effect to be concentrated in the affected tissues. The doses of nucleic acid sequences used may be adapted in accordance with various parameters, and in particular in accordance with the vector, the mode of administration used, the pathology in question or the desired treatment period.

4. Document ID: US 6172043 B1

L10: Entry 4 of 42

File: USPT

Jan 9, 2001

US-PAT-NO: 6172043

DOCUMENT-IDENTIFIER: US 6172043 B1

TITLE: Treatments for neurotoxicity in Alzheimer's disease caused by .beta. amyloid peptides

DATE-ISSUED: January 9, 2001

US-CL-CURRENT: 514/17; 514/13, 514/14, 514/15, 514/16, 530/325, 530/326, 530/327, 530/328, 530/329, 530/330

APPL-NO: 9/005215

DATE FILED: January 9, 1998

PARENT-CASE:

RELATED APPLICATIONS This application claims priority under 35 U.S.C. .sctn. 119 from U.S. provisional application Ser. No. 60/035,847, filed Jan. 10, 1997 and which is a continuation in part of U.S. Ser. No. 08/960,188 filed Oct. 29, 1997 now abandoned.

IN: Ingram; Vernon M., Blanchard; Barbara J.

AB: The invention involves identification of a mechanism of .beta.-amyloid peptide cytotoxicity, which enables treatment of conditions caused by .beta.-amyloid peptide aggregates by administration of compounds which antagonize the mechanism of cytotoxicity.

The invention includes the identification and isolation of compounds which can antagonize the aggregation of .beta.-amyloid peptides and the neurotoxic effects of such aggregates.

The compounds include isolated peptides which were selected for their ability to form a complex with a .beta.-amyloid peptide, or are derived from peptides so selected. Methods for treating conditions resulting from neurotoxic .beta.-amyloid peptide aggregates and pharmaceutical preparations are provided. Also provided are methods for selecting additional compounds which can antagonize the aggregation of .beta.-amyloid

peptides and the neurotoxic
effects of such aggregates.

L10: Entry 4 of 42

File: USPT

Jan 9, 2001

DOCUMENT-IDENTIFIER: US 6172043 B1
TITLE: Treatments for neurotoxicity in Alzheimer's disease caused by .beta. amyloid peptides

DEPR:
The assay mixture also comprises a candidate pharmacological agent. Typically, a plurality of
assay mixtures are run in parallel with different agent concentrations to obtain a different
response to the various concentrations. Typically, one of these concentrations serves as a
negative control, i.e., at zero concentration of agent or at a concentration of agent below the
limits of assay detection. Candidate agents encompass numerous chemical classes, although
typically they are organic compounds. Preferably, the candidate pharmacological agents are small
organic compounds, i.e., those having a molecular weight of more than 50 yet less than about
2500. Candidate agents comprise functional chemical groups necessary for structural interactions
with polypeptides, and typically include at least an amine, carbonyl, hydroxyl or carboxyl group,
preferably at least two of the functional chemical groups and more preferably at least three of
the functional chemical groups. The candidate agents can comprise cyclic carbon or heterocyclic
structure and/or aromatic or polyaromatic structures substituted with one or more of the
above-identified functional groups. Candidate agents also can be biomolecules such as peptides,
saccharides, fatty acids, sterols, isoprenoids, purines, pyrimidines, derivatives or structural
analogs of the above, or combinations thereof and the like. Where the agent is a nucleic acid,
the agent typically is a DNA or RNA molecule, although modified nucleic acids having non-natural
bonds or subunits are also contemplated.

DEPR:
The therapeutics of the invention can be administered by any conventional route, including
injection or by gradual infusion over time. The administration may, for example, be oral,
intravenous, intracranial, intraperitoneal, intramuscular, intracavity, intrarespiratory,
subcutaneous, or transdermal. The route of administration will depend on the composition of a
particular therapeutic preparation of the invention.

5. Document ID: US 6159731 A

L10: Entry 5 of 42

File: USPT

Dec 12, 2000

US-PAT-NO: 6159731
DOCUMENT-IDENTIFIER: US 6159731 A
TITLE: Daxx, a Fas-binding protein that activates JNK and apoptosis
DATE-ISSUED: December 12, 2000

US-CL-CURRENT: 435/325; 435/320.1, 435/357, 435/367, 435/369, 435/440, 435/69.1, 530/350,
536/23.1, 536/23.5, 536/24.31 , 536/24.33

APPL-NO: 9/ 022983
DATE FILED: February 12, 1998

PARENT-CASE:
RELATED APPLICATIONS This application claims benefit of U.S. provisional application Ser. No.
60/037,919, filed filed Feb. 12, 1997 and U.S. provisional application Ser. No. 60/051,753, filed
filed Jun. 26, 1997.

IN: Yang; Xiaolu, Khosravi-Far; Roya, Chang; Howard Y., Baltimore; David

AB: The invention describes nucleic acids encoding the Daxx protein, including
fragments and biologically functional variants thereof. Also included are polypeptides and
fragments thereof encoded by such nucleic acids, and antibodies relating thereto. Methods
and products for using such nucleic acids and polypeptides also are provided.

L10: Entry 5 of 42

File: USPT

Dec 12, 2000

DOCUMENT-IDENTIFIER: US 6159731 A
TITLE: Daxx, a Fas-binding protein that activates JNK and apoptosis

DEPR:
The therapeutics of the invention can be administered by any conventional route, including
injection or by gradual infusion over time. The administration may, for example, be oral,
intravenous, intraperitoneal, intramuscular, intracavity, subcutaneous, or transdermal. When
antibodies are used therapeutically, a preferred route of administration is by pulmonary aerosol.
Techniques for preparing aerosol delivery systems containing antibodies are well known to those
of skill in the art. Generally, such systems should utilize components which will not
significantly impair the biological properties of the antibodies, such as the paratope binding
capacity (see, for example, Sciarra and Cutie, "Aerosols," in Remington's Pharmaceutical
Sciences, 18th edition, 1990, pp 1694-1712; incorporated by reference). Those of skill in the art
can readily determine the various parameters and conditions for producing antibody aerosols
without resort to undue experimentation. When using antisense preparations of the invention, slow
intravenous administration is preferred.

DEPR:
The assay mixture also comprises a compound. Typically, a plurality of assay mixtures are run in
parallel with different agent concentrations to obtain a different response to the various
concentrations. Typically, one of these concentrations serves as a negative control, i.e., at
zero concentration of agent or at a concentration of agent below the limits of assay detection.
Candidate compounds encompass numerous chemical classes, although typically they are organic
compounds. Preferably, the candidate compounds are small organic compounds, i.e., those having a
molecular weight of more than 50 yet less than about 2500, preferably less than about 1000 and,
more preferably, less than about 500. Candidate compounds comprise

functional chemical groups
necessary for structural interactions with polypeptides and/or nucleic acids, and typically
include at least an amine, carbonyl, hydroxyl or carboxyl group, preferably at least two of the
functional chemical groups and more preferably at least three of the functional chemical groups.
The candidate compounds can comprise cyclic carbon or heterocyclic structure and/or aromatic or
polyaromatic structures substituted with one or more of the above-identified functional groups.
Candidate compounds also can be biomolecules such as peptides, saccharides, fatty acids, sterols,
isoprenoids, purines, pyrimidines, derivatives or structural analogs of the above, or
combinations thereof and the like. Where the compounds is a nucleic acid, the agent typically is
a DNA or RNA molecule, although modified nucleic acids as defined herein are also contemplated.

DEPR:
Various techniques may be employed for introducing nucleic acids of the invention into cells,
depending on whether the nucleic acids are introduced in vitro or in vivo in a host. Such
techniques include transfection of nucleic acid-CaPO.sub.4 precipitates, transfection of nucleic
acids associated with DEAE, transfection with a retrovirus including the nucleic acid of
interest, liposome mediated transfection, and the like. For certain uses, it is preferred to
target the nucleic acid to particular cells. In such instances, a vehicle used for delivering a
nucleic acid of the invention into a cell (e.g., a retrovirus, or other virus; a liposome) can
have a targeting molecule attached thereto. For example, a molecule such as an antibody specific
for a surface membrane protein on the target cell or a ligand for a receptor on the target cell
can be bound to or incorporated within the nucleic acid delivery vehicle. For example, where
liposomes are employed to deliver the nucleic acids of the invention, proteins which bind to a
surface membrane protein associated with endocytosis may be incorporated into the liposome
formulation for targeting and/or to facilitate uptake. Such proteins include capsid proteins or
fragments thereof tropic for a particular cell type, antibodies for proteins which undergo
internalization in cycling, proteins that target intracellular localization and enhance
intracellular half life, and the like. Polymeric delivery systems also have been used
successfully to deliver nucleic acids into cells, as is known by those skilled in the art. Such
systems even permit oral delivery of nucleic acids.

6. Document ID: US 6143561 A

L10: Entry 6 of 42

File: USPT

Nov 7, 2000

US-PAT-NO: 6143561
DOCUMENT-IDENTIFIER: US 6143561 A
TITLE: DNA encoding plastid pyruvate dehydrogenase and branched chain oxoacid dehydrogenase
components
DATE-ISSUED: November 7, 2000

US-CL-CURRENT: 435/419; 435/252.3, 435/320.1, 536/23.2, 536/23.6

APPL-NO: 9/ 108020
DATE FILED: June 30, 1998

PARENT-CASE:
This application claims the benefit of priority of the following Provisional patent applications:
Serial No. 60/051,291, filed Jun. 30, 1997; Ser. No. 60/055,255, filed Aug. 1, 1997; Ser. No.
60/076,544, filed Mar. 2, 1998; and Ser. No. 60/076,554, filed Mar. 2, 1998.

IN: Randall; Douglas D., Mooney; Brian P., Johnston; Mark L., Luethy; Michael H.,
Miernyk; Jan A.

AB: Provided are nucleic acid sequences encoding E1.alpha., E1.beta., and E2 subunits
of plastid pyruvate dehydrogenase complexes and branched chain oxoacid dehydrogenase
complexes.

L10: Entry 6 of 42

File: USPT

Nov 7, 2000

DOCUMENT-IDENTIFIER: US 6143561 A
TITLE: DNA encoding plastid pyruvate dehydrogenase and branched chain oxoacid dehydrogenase
components

BSPR:
As noted above, P(3HB-co-3HV) random copolymer, commercially known as Biopol.TM., is produced by
fermentation employing A. eutrophus. A proposed biosynthetic pathway for P(3HB-co-3HV) copolymer
production is shown in FIG. 2. Production of this polymer in plants has been reported (oral
presentation by Mitsky et al., 1997).

DEPR:
All of the enzymes discussed herein can be modified for plastid targeting by employing plant cell
nuclear transformation constructs wherein DNA coding sequences of interest are fused to any of
the available transit peptide sequences capable of facilitating transport of the encoded enzymes
into plant plastids (partially summarized in von Heijne et al., 1991), and driving expression by
employing an appropriate promoter. The sequences that encode a transit peptide region can be
obtained, for example, from plant nuclear-encoded plastid proteins, such as the small subunit
(SSU) of ribulose bisphosphate carboxylase, plant fatty acid biosynthesis related genes including
acyl carrier protein (ACP), stearoyl-ACP desaturase, .beta.-ketoacyl-ACP synthase and acyl-ACP
thioesterase, or LHCPII genes. The encoding sequence for a transit peptide effective in transport
to plastids can include all or a portion of the encoding sequence for a particular transit
peptide, and may also contain portions of the mature protein encoding sequence associated with a
particular transit peptide. Numerous examples of transit peptides that can be used to deliver
target proteins into plastids exist, and the particular transit peptide encoding sequences useful
in the present invention are not critical as long as delivery into a plastid is obtained.
Proteolytic processing within the plastid then produces the mature enzyme. This technique has
proven successful not only with enzymes involved in PHA synthesis (Nawrath et al., 1994), but
also with neomycin phosphotransferase II (NPT-II) and CP4 EPSPS (Padgette et al., 1995), for

example.

DEPR:
2. By creating a plant transformation vector comprising a coding sequence for the enzyme operably
linked to a plastid targeting sequence, then transforming this vector into the plant. All of the
enzymes discussed herein can be modified for plastid targeting by employing plant cell nuclear
transformation constructs wherein DNA coding sequences of interest are fused to any of the
available targeting peptide sequences capable of facilitating transport of the encoded enzymes
into plant plastids, and driving expression by employing an appropriate promoter. Examples of
plastid targeting peptides are provided in Table 1 and in von Heijne et al. (1991). The sequences
that encode a targeting peptide region can be obtained, for example, from plant nuclear-encoded
plastid proteins, such as the small subunit (SSU) of ribulose bisphosphate carboxylase, plant
fatty acid biosynthesis related genes including acyl carrier protein (ACP), stearoyl-ACP
desaturase, .beta.-ketoacyl-ACP synthase and acyl-ACP thioesterase, or LHCPII genes. The encoding
sequence for a targeting peptide effective in transport to plastids can include all or a portion
of the encoding sequence for a particular targeting peptide, and can also contain portions of the
mature protein encoding sequence associated with a particular targeting peptide. Numerous
examples of targeting peptides that can be used to deliver target proteins into plastids exist,
and the particular targeting peptide encoding sequences useful in the present invention are not
critical as long as delivery into a plastid is obtained. Proteolytic processing within the
plastid then produces the mature enzyme. This technique has proven successful not only with
enzymes involved in PHA synthesis (Nawrath et al., 1994), but also with neomycin
phosphotransferase II (NPT-II) and CP4 EPSPS (Padgette et al., 1995), for example.

7. Document ID: US 6143530 A

L10: Entry 7 of 42
File: USPT
Nov 7, 2000

US-PAT-NO: 6143530
DOCUMENT-IDENTIFIER: US 6143530 A
TITLE: Circular DNA expression cassettes for in vivo gene transfer
DATE-ISSUED: November 7, 2000

US-CL-CURRENT: 435/91.42; 435/252.3, 435/252.33, 435/254.11, 435/320.1, 435/325, 435/455, 435/91.1, 435/91.4, 514/44

APPL-NO: 8/ 894511
DATE FILED: August 19, 1997

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
FR	95 02117	February 23, 1995

PCT-DATA:

APPL-NO	DATE-FILED	PUB-NO	PUB-DATE	371-DATE	102(E)-DATE
PCT/FR96/00274	February 21, 1996	WO96/26270	Aug 29, 1996	Aug 19, 1997	Aug 19, 1997

IN: Crouzet; Joel, Scherman; Daniel, Cameron; Beatrice, Wils; Pierre, Darquet; Anne-Marie

AB: Double-stranded DNA molecules characterised in that they are circular and in that
they essentially include one or more genes of interest.

L10: Entry 7 of 42
File: USPT
Nov 7, 2000

DOCUMENT-IDENTIFIER: US 6143530 A
TITLE: Circular DNA expression cassettes for in vivo gene transfer

BSPR:
In this connection, another subject of the present invention relates to any pharmaceutical
composition comprising at least one DNA molecule as defined above. This molecule may be naked or
combined with a chemical and/or biochemical transfection vector. The pharmaceutical compositions
according to the invention may be formulated with a view to topical, oral, parenteral,
intranasal, intravenous, intramuscular, subcutaneous, intra-ocular, transdermal, and the like,
administration. Preferably, the DNA molecule is used in an injectable form or by application. It
may be mixed with any pharmaceutically acceptable vehicle for an injectable formulation, in
particular for a direct injection at the site to be treated. The compositions can be, in
particular, in the form of isotonic sterile solutions, or of dry, in particular lyophilized
compositions which, on addition of sterilized water or physiological saline as appropriate,
enable injectable solutions to be made up. Diluted Tris or PBS buffers in glucose or sodium
chloride may be used in particular. A direct injection of the nucleic acid into the affected
region of the patient is advantageous, since it enables the therapeutic effect to be concentrated
in the tissues affected. The doses of nucleic acid used may be adapted in accordance with
different parameters, and in particular in accordance with the gene, the vector, the mode of
administration used, the pathology in question or alternatively the desired treatment period.

BSPR:
Generally, in the plasmids and molecules of the invention, the gene of therapeutic, vaccinal,
agricultural or veterinary value also contains a transcription promoter region which is
functional in the target cell or body (i.e. mammals), as well as a region located at the 3' end
and which specifies a transcription termination signal and a polyadenylation site (expression
cassette). As regards the promoter region, this can be a promoter region

naturally responsible
for the expression of the gene in question when the latter is capable of functioning in the cell
or body in question. The promoter regions can also be those of different origin (responsible for
the expression of other proteins, or even synthetic promoters). In particular, the promoter
sequences can be from eukaryotic or viral genes. For example, they can be promoter sequences
originating from the genome of the target cell. Among eukaryotic promoters, it is possible to use
any promoter or derived sequence that stimulates or represses the transcription of a gene,
specifically or otherwise, inducibly or otherwise, strongly or weakly. They can be, in
particular, ubiquitous promoters (promoter of the HPRT, PGK, .alpha.-actin, tubulin, and the
like, genes), promoters of intermediate filaments (promoter of the GFAP, desmin, vimentin,
neurofilament, keratin, and the like, genes), promoters of therapeutic genes (for example the
promoter of the MDR, CFTR, factor VIII, ApoAI, and the like, genes), tissue-specific promoters
(promoter of the pyruvate kinase gene, villin gene, gene for intestinal fatty acid binding
protein, gene for .alpha.-actin of smooth muscle, and the like) or alternatively promoters that
respond to a stimulus (steroid hormone receptor, retinoic acid receptor, and the like).
Similarly, the promoter sequences may be those originating from the genome of a virus, such as,
for example, the promoters of the adenovirus E1A and MLP genes, the CMV early promoter or
alternatively the RSV LTR promoter, and the like. In addition, these promoter regions may be
modified by the addition of activator or regulator sequences or sequences permitting a
tissue-specific or -preponderant expression.

8. Document ID: US 6127175 A

L10: Entry 8 of 42
File: USPT
Oct 3, 2000

US-PAT-NO: 6127175
DOCUMENT-IDENTIFIER: US 6127175 A
TITLE: Cells for the production of recombinant adenoviruses
DATE-ISSUED: October 3, 2000

US-CL-CURRENT: 435/325; 424/199.1, 435/235.1, 435/320.1, 435/366, 435/69.1, 435/91.1, 435/91.41,
514/44, 536/23.72, 536/24.1

APPL-NO: 8/ 875223
DATE FILED: July 17, 1997

FOREIGN-APPL-PRIORITY-DATA:
COUNTRY APPL-NO APPL-DATE
FR 95 00747 January 20, 1995
FR 95 06532 June 1, 1995
FR 95 10541 September 8, 1995

PCT-DATA:
APPL-NO DATE-FILED PUB-NO PUB-DATE 371-DATE 102(E)-DATE
PCT/FR96/00088 January 19, 1996 WO96/22378 Jul 25, 1996 Jul 17, 1997 Jul 17, 1997

IN: Vigne; Emmanuelle, Perricaudet; Michel, Dedieu; Jean-Fran.cedilla.ois, Orsini;
Cecile, Yeh; Patrice, Latta; Martine, Prost; Edouard

AB: The invention relates to cells usable for the production of defective
adenoviruses comprising, inserted into their genome, a portion of the region E4 of an
adenovirus genome carrying the reading phase ORF6 under the control of a functional
promoter.

L10: Entry 8 of 42
File: USPT
Oct 3, 2000

DOCUMENT-IDENTIFIER: US 6127175 A
TITLE: Cells for the production of recombinant adenoviruses

BSPR:
Generally, the heterologous nucleic acid sequence also comprises a transcription promoter region
which is functional in the infected cell, as well as a region situated in 3' of the gene of
interest, and which specifies a transcriptional end signal and a polyadenylation site. All of
these elements constitute the expression cassette. As regards the promoter region, it may be a
promoter region which is naturally responsible for the expression of the considered gene when the
said promoter region is capable of functioning in the infected cell. It may also be regions of
different origin (which are responsible for the expression of other proteins, or which are even
synthetic). In particular, they may be promoter sequences of eukaryotic or viral genes or any
promoter or derived sequence, stimulating or repressing the transcription of a gene in a specific
manner or otherwise and in an inducible manner or otherwise. By way of example, they may be
promoter sequences derived from the genome of the cell which it is desired to infect, or of the
genome of a virus, especially the promoters of the adenovirus MLP, E1A genes, the RSV-LTR, CMV
promoter, and the like. Among the eukaryotic promoters, there may also be mentioned the
ubiquitous promoters (HPRT, vimentin, .alpha.-actin, tubilin and the like), the promoters of the
intermediate filaments (desmin, neurofilaments, keratin, GFAP and the like), the promoters of
therapeutic genes (MDR, CFTR, factor VIII type and the like), the tissue-specific promoters
(pyruvate kinase, villin, the promoter for the intestinal fatty acid-binding protein, the
promoter for .alpha.-actin of the smooth muscle cells, promoters specific for the liver; ApoAI,
ApoAII, human albumin and the like) or alternatively the promoters which respond to a stimulus
(steroid hormone receptor, retinoic acid receptor and the like). In addition

these expression
sequences may be modified by the addition of activating or regulatory sequences or of sequences
allowing a tissue-specific or predominant expression. Moreover, when the inserted nucleic acid
does not contain expression sequences, it may be inserted into the genome of the defective virus
downstream of such a sequence.

BSPR:
The present invention also relates to the purified viral preparations (adenovirus and AAV)
obtained according to the process of the invention, as well as any pharmaceutical composition
comprising one or more defective recombinant adenoviruses or AAVs prepared according to this
process. The pharmaceutical compositions of the invention can be formulated for a topical, oral,
parenteral, intranasal, intravenous, intramuscular, subcutaneous, intraocular or transdermal
administration and the like.

9. Document ID: US 6121005 A

L10: Entry 9 of 42

File: USPT

Sep 19, 2000

US-PAT-NO: 6121005
DOCUMENT-IDENTIFIER: US 6121005 A
TITLE: Polypeptides comprising domains of the GAX protein implicated in the repression of
transcription and/or interaction with other proteins, corresponding nucleic acids, and their use
DATE-ISSUED: September 19, 2000

US-CL-CURRENT: 435/7.1; 530/324, 530/350

APPL-NO: 8/950860
DATE FILED: October 15, 1997

FOREIGN-APPL-PRIORITY-DATA:
COUNTRY APPL-NO APPL-DATE
FR 96 12730 October 18, 1996

IN: Fournier; Alain, Mahfoudi; Abderrahim, Marcireau; Christophe, Branellec; Didier

AB: This invention pertains to polynucleotides comprising GAX domains involved in GAX
biological activity. It may pertain, notably, to domains involved in the interaction of GAX
with other molecules or domains that are responsible for biological activity. The invention
also pertains to chimeric molecules comprising a GAX functional domain. It also pertains to
the use of GAX to repress gene expression, as well as the use of compounds that inhibit GAX
interaction with certain cellular partners to modulate GAX activity. It also pertains to a
method for screening and/or identifying GAX cellular partners.

L10: Entry 9 of 42

File: USPT

DOCUMENT-IDENTIFIER: US 6121005 A
TITLE: Polypeptides comprising domains of the GAX protein implicated in the repression of
transcription and/or interaction with other proteins, corresponding nucleic acids, and their use

BSPR:
The promoter is advantageously selected from among the functional promoters in human cells. More
preferably, it is a promoter that permits the expression of a nucleic acid sequence in a
hyperproliferative cell (cancer cells, restenosis, etc.). In this regard, different promoters may
be used. Thus, it can be any promoter or derived sequence that stimulates or represses the
transcription of a gene in a specific or non-specific, inducible or non-inducible, strong or weak
manner. Notably, we can cite promoter sequences of eukaryotic or viral genes. For example, they
may be promoter sequences from the genome of the target cell. Among the eukaryotic promoters,
ubiquitous promoters, in particular, can be used (HPRT [hypoxanthine-guanine-phosphoribosyl
transferase], PGK [phosphoglycerate kinase], alpha-actin, tubulin, DHFR [dihydrofolate
reductase], etc. gene promoters), intermediary filaments promoters (promoter of GFAP [glial
fibrillary acidic protein], desmin, vimentin, neurofilaments, keratin, etc. genes), promoters of
therapeutic genes (for example, the promoter of MDR and CFTR [cystic fibrosis transmembrane
regulator] genes, Factor VIII, ApoAI, etc.), specific tissue promoters (the promoter of the
pyruvate kinase gene, villin, intestinal fatty acids binding protein, smooth muscle alpha-actin,
etc.), specific cell promoters of types of dividing cells, such as cancer cells or even promoters
that respond to a stimulus (steroid hormones receptor, retinoic acid receptor, glucocorticoid
receptor, etc.) or so-called inducible [promoters]. In like manner, they may be promoter
sequences from a virus genome, such as for example, promoters of adenovirus E1A and MLP genes,
the early CMV [cytomegalovirus] promoter, or even the LTR [long terminal repeat] promoter of the
RSV [respiratory synctial virus], etc. Moreover, these promoter regions may be modified by the
addition of activating or

BSPR:
The nucleic acid or the vector used in this invention can be formulated with a view to topical,
oral, parenteral, intranasal, intravenous, intramuscular, subcutaneous, intraocular, transdermal,
etc. administration. Preferably, the nucleic acid or the vector is used in an injectable form.
Therefore, it can be mixed with any vehicle that is pharmaceutically acceptable for an injectable
formulation, notably for a direct injection into the site to be treated. In particular, it may be
in the form of sterile, isotonic solutions or dry compositions, notably freeze-dried
compositions, which after the addition of sterilized water or physiological serum, as the case
may be, constitute injectable solutes. The doses of the nucleic acid used may be adapted in terms
of the different parameters, and notably, as a function of the gene, the vector, the method of
administration used, the pathology in question, or even the desired duration of the treatment.

BSPR:
Because of their antiproliferative properties, the pharmaceutical compositions according to the

invention are particularly well-suited for the treatment of hyperproliferative disorders, such as
notably, cancers and restenosis. Thus, this invention provides a particularly efficacious method
for the destruction of cells, notably hyperproliferative cells. It is, therefore, applicable to
the destruction of tumor cells or to the smooth muscle cells of the vascular wall (restenosis).
It is very particularly suited to the treatment of cancers. As an example, we can cite
adenocarcinomas of the colon, thyroid cancers, carcinoma of the lungs, myeloid leukemias,
colorectal cancers, breast cancer, lung cancer, stomach cancers, esophageal cancers, B lymphomas,
ovarian cancers, bladder cancers, glioblastomas, hepatocarcinomas, cancers of bone, skin,
pancreas or even kidney and prostate cancers, cancers of the esophagus, cancers of the larynx,
cancers of the head and neck, HPV [human papilloma virus] positive anogenital cancers, EBV
[Epstein-Barr virus] positive nasopharynx cancers, etc.

10. Document ID: US 6114322 A

L10: Entry 10 of 42

File: USPT

Sep 5, 2000

US-PAT-NO: 6114322
DOCUMENT-IDENTIFIER: US 6114322 A
TITLE: Hypolipidemic 1,4-benzothiazepine-1,1-dioxides
DATE-ISSUED: September 5, 2000

US-CL-CURRENT: 514/211.01; 540/552

APPL-NO: 9/ 361530
DATE FILED: July 27, 1999

PARENT-CASE:
This application is a division of U.S. Pat. No. 09/041,953 filed Mar. 13, 1998, U.S. Pat. No.
6,020,331.

FOREIGN-APPL-PRIORITY-DATA:
COUNTRY
APPL-NO
APPL-DATE
EP
97104348
March 14, 1997

IN: Enhsen; Alfons, Falk; Eugen, Glombik; Heiner, Stengelin; Siegfried

AB: The present invention is concerned with new hypolipidemic compounds, with
processes and novel intermediates for their preparation, with pharmaceutical compositions
containing them and with their use in medicine, particularly in the prophylaxis and
treatment of hyperlipidemic conditions, such as atherosclerosis., Compounds of the formula
(I): ##STR1## wherein R.sup.1 to R.sup.10 and X are as defined in the Specification and
useful as hypolipidemic compounds.

L10: Entry 10 of 42

File: USPT

DOCUMENT-IDENTIFIER: US 6114322 A
TITLE: Hypolipidemic 1,4-benzothiazepine-1,1-dioxides

BSPR:
Pharmaceutical compositions according to the present invention include those suitable for oral,
rectal, topical, buccal (e.g. sub-lingual) and parenteral (e.g. subcutaneous, intramuscular,
intradermal, or intravenous) administration, although the most suitable route in any given case
will depend on the nature and severity of the condition being treated and on the nature of the
particular compound of formula (I) which is being used. Enteric-coated and enteric-coated
controlled release formulations are also within the scope of the invention. Preferred are acid
and gastric juice resistant formulations. Suitable enteric coatings include cellulose acetate
phthalate, polyvinylacetate phthalate, hydroxypropylmethylcellulose phthalate and anionic
polymers of methacrylic acid and methacrylic acid methyl ester.

BSPR:
Pharmaceutical compositions suitable for oral administration can be presented in discrete units,
such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of a
compound of formula (I); as a powder or granules; as a solution or a suspension in an aqueous or
non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. As indicated, such
compositions can be prepared by any suitable method of pharmacy which includes the step of
bringing into association the active compound and the carrier (which can constitute one or more
accessory ingredients). In general, the compositions are prepared by uniformly and intimately
admixing the active compound with a liquid or finely divided solid carrier, or both, and then, if
necessary, shaping the product. For example, a tablet can be prepared by compressing or moulding
a powder or granules of the compound, optionally with one or more accessory ingredients.
Compressed tablets can be prepared by compressing, in a suitable machine, the compound in a
free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert
diluent and/or surface active/dispersing agent(s). Moulded tablets can be made by moulding, in a
suitable machine, the powdered compound moistened with an inert liquid diluent.

BSPR:
Pharmaceutical compositions suitable for rectal administration are preferably presented as
unit-dose suppositories. These can be prepared by admixing a compound of formula (I) with one or
more conventional solid carriers, for example, cocoa butter, and then shaping the resulting
mixture.

BSPR:
In order to prove the greater hypolipidemic activity of the compounds according to the invention
tests were carried out by means of three genetically modified cell lines. These were derivatives
of the generally known "Chinese hamster ovary" (CHO) cell line, which on account of incorporated
expression plasmids additionally produced sodium-dependent bile acid transporters. The first cell
line (CHO/pRIBAT8) was in this case the ileal transporter of the rabbit (RIBAT), the second
(CHO/pHIBAT8) the ileal transporter of the human (HIBAT) and the third (CHO/pHLBAT5) the hepatic

transporter of the human. All plasmids were based on the standard plasmid pCDNA1 new, which as
important elements has a cytomegaloviral promoter for the permanent expression of heterologous
genes and a gene for the production of cell resistance against the substance G418.

BSPR:
For the preparation of the genetically modified cell lines, CHO cells were transfected with DNA
from pRIBAT8, pHIBAT8 or pHLBAT5 and cells which developed resistance against the selection
substance G418 were selectively additionally cultured by addition of the substance to the cell
medium. The cells CHO/pRIBAT8, CHO/pHIBAT8 and CHO/pHLBAT5 were then isolated from the amount of
G418-resistant cells and pure clonal lines were cultured therefrom. The tool used for following
the isolation process was in this case a fluorescent bile acid derivative (3.beta.-NBD-NCT;
N-[7-(4-nitrobenzo-2-oxa-1,3-diazol)]-3.beta.-amino-7a,
12a-dihydroxy-5.beta.-cholan-24-oyl)-2'-aminoethanesulfonate. Cells with intact bile acid
transporters rapidly absorbed this substance from the cell medium and as a result became
fluorescent. They could thereby be easily differentiated from cells without intact bile acid
transporters with the aid of a fluorescence microscope.

11. Document ID: US 6103869 A

L10: Entry 11 of 42

File: USPT

Aug 15, 2000

US-PAT-NO: 6103869
DOCUMENT-IDENTIFIER: US 6103869 A
TITLE: Smad2 phosphorylation and interaction with Smad4
DATE-ISSUED: August 15, 2000

US-CL-CURRENT: 530/330; 530/300, 530/326, 530/327, 530/328, 530/329, 530/350

APPL-NO: 9/082039
DATE FILED: May 20, 1998

PARENT-CASE:
RELATED APPLICATIONS This application claims priority under 35 U.S.C. .sctn.119 from U.S.
provisional application Ser. No. 60/047,807, filed May 20, 1997, and from U.S. provisional
application Ser. No. 60/081,313, filed Apr. 10, 1998.

IN: Souchelnytokyi; Serhiy, Tamaki; Kiyoshi, Engetrom; Ulla, Wernstedt; Christer,
Piek; Ester, ton Dijke; Peter, Heldin; Carl-Henrik

AB: The invention describes amino acid residues of the Smad2 protein which are
important for phosphorylation and activity, and Smad2 polypeptide fragments and biologically
functional variants thereof. Included and dominant-negative variants of Smad2 and antibodies
relating thereto. Also included are nucleic acids which encode such variants. Antibodies
which selectively bind pathway-restricted Smad proteins phosphorylated at the C-terminal
tail also are provided. Methods and products for using such nucleic acids and polypeptides
also are provided.

L10: Entry 11 of 42

File: USPT

Aug 15, 2000

DOCUMENT-IDENTIFIER: US 6103869 A
TITLE: Smad2 phosphorylation and interaction with Smad4

DEPR:
The therapeutics of the invention can be administered by any conventional route, including
injection or by gradual infusion over time. The administration may, for example, be oral,
intravenous, intraperitoneal, intramuscular, intracavity, subcutaneous, or transdermal. When
antibodies are used therapeutically, a preferred route of administration is by pulmonary aerosol.
Techniques for preparing aerosol delivery systems containing antibodies are well known to those
of skill in the art. Generally, such systems should utilize components which will not
significantly impair the biological properties of the antibodies, such as the paratope binding
capacity (see, for example, Sciarra and Cutie, "Aerosols," in Remington's Pharmaceutical
Sciences, 18th edition, 1990, pp 1694-1712; incorporated by reference). Those of skill in the art
can readily determine the various parameters and conditions for producing antibody aerosols
without resort to undue experimentation. When using antisense preparations of the invention, slow
intravenous administration is preferred.

DEPR:
The assay mixture also comprises a candidate pharmacological agent. Typically, a plurality of
assay mixtures are run in parallel with different agent concentrations to obtain a different
response to the various concentrations. Typically, one of these concentrations serves as a
negative control, i.e., at zero concentration of agent or at a concentration of agent below the
limits of assay detection. Candidate agents encompass numerous chemical classes, although
typically they are organic compounds. Preferably, the candidate pharmacological agents are small
organic compounds, i.e., those having a molecular weight of more than 50 yet less than about
2500, preferably less than about 1000 and, more preferably, less than about 500. Candidate agents
comprise functional chemical groups necessary for structural interactions with polypeptides
and/or nucleic acids, and typically include at least an amine, carbonyl, hydroxyl or carboxyl
group, preferably at least two of the functional chemical groups and more preferably at least
three of the functional chemical groups. The candidate agents can comprise cyclic carbon or
heterocyclic structure and/or aromatic or polyaromatic structures substituted with one or more of
the above-identified functional groups. Candidate agents also can be biomolecules such as
peptides, saccharides, fatty acids, sterols, isoprenoids, purines, pyrimidines, derivatives or
structural analogs of the above, or combinations thereof and the like. Where the agent is a
nucleic acid, the agent typically is a DNA or RNA molecule, although modified nucleic acids as
defined herein are also contemplated.

DEPR:
example, a molecule such as an antibody specific for a surface membrane protein on the target
cell or a ligand for a receptor on the target cell can be bound to or incorporated within the
nucleic acid delivery vehicle. For example, where liposomes are employed

to deliver the nucleic
acids of the invention, proteins which bind to a surface membrane protein associated with
endocytosis may be incorporated into the liposome formulation for targeting and/or to facilitate
uptake. Such proteins include capsid proteins or fragments thereof tropic for a particular cell
type, antibodies for proteins which undergo internalization in cycling, proteins that target
intracellular localization and enhance intracellular half life, and the like. Polymeric delivery
systems also have been used successfully to deliver nucleic acids into cells, as is known by
those skilled in the art. Such systems even permit oral delivery of nucleic acids.

12. Document ID: US 6093692 A

L10: Entry 12 of 42

File: USPT

Jul 25, 2000

US-PAT-NO: 6093692
DOCUMENT-IDENTIFIER: US 6093692 A
TITLE: Method and compositions for lipidization of hydrophilic molecules
DATE-ISSUED: July 25, 2000

US-CL-CURRENT: 514/3; 514/19, 514/2, 514/23, 514/9, 530/300, 530/303, 530/307, 530/315, 530/317,
530/331, 530/333, 530/350

APPL-NO: 8/ 936898
DATE FILED: September 25, 1997

PARENT-CASE:
This application claims the benefit of provisional applications 60/077,177, filed Sep. 26, 1996,
and 60/049,499, filed Jun. 13, 1997.

IN: Shen; Wei-Chiang, Wang; Jinghua

AB: Fatty acid derivatives of disulfide-containing compounds (for example,
disulfide-containing peptides or proteins) comprising fatty acid-conjugated products with a
disulfide linkage are employed for delivery of the compounds to mammalian cells. This
modification markedly increases the absorption of the compounds by mammalian cells relative
to the rate of absorption of the unconjugated compounds, as well as prolonging blood and
tissue retention of the compounds. Moreover, the disulfide linkage in the conjugate is quite
labile in vivo and thus facilitates intracellular or extracellular release of the intact
compounds from the fatty acid moieties.

L10: Entry 12 of 42

File: USPT

Jul 25, 2000

DOCUMENT-IDENTIFIER: US 6093692 A
TITLE: Method and compositions for lipidization of hydrophilic molecules

BSPR:
Such alternative routes may include the buccal, nasal, oral, pulmonary, rectal and ocular routes.

Without exception, these routes are less effective than the parenteral routes of administration,
but are still far more attractive than the parenteral routes because they offer convenience and
control to the patients. The oral route is particularly attractive because it is the most
convenient and patient-compliant.

BSPR:
Mucosal barriers, which separate the inside of the body from the outside (e.g. GI, ocular,
pulmonary, rectal and nasal mucosa), comprise a layer of tightly joined cell monolayers which
strictly regulate the transport of molecules. Individual cells in barriers are joined by tight
junctions which regulate entry into the intercellular space. Hence, the mucosa is at the first
level a physical barrier, transport through which depends on either the transcellular or the
paracellular pathways [Lee, V. H. L., CRC. Critical Rev. Ther. Drug Delivery Sys., 5:69-97
(1988)].

BSPR:
In addition to providing a tight physical barrier to the transport of proteins and peptides,
mucosal barriers possess enzymes which can degrade proteins and peptides before, after, and
during their passage across the mucosa. This barrier is referred to as the enzymatic barrier. The
enzymatic barrier consists of endo- and exopeptidase enzymes which cleave proteins and peptides
at their terminals or within their structure. Enzymatic activity of several mucosa have been
studied and the results demonstrated that substantial protease activity exists in the homogenates
of buccal, nasal, rectal and vaginal mucosa of albino rabbits and that these activities are
comparable to those present in the ilium [Lee, et al., (1988), supra]. Therefore, regardless of
the mucosa being considered, the enzymatic barrier present will feature strongly in the
degradation of the protein and peptide molecules.

BSPR:
In accordance with the present invention, fatty acid derivatives of sulfhydryl- or
disulfide-containing compounds (for example, peptides, proteins or oligonucleotides which contain
or are modified to contain sulfhydryl groups) comprising fatty acid-conjugated products with
disulfide linkage(s) are employed for delivery of the sulfhdryl- or disulfide-containing
compounds to mammalian cells. This modification markedly increases the absorption of the
compounds by mammalian cells relative to the rate of absorption of the unconjugated compounds, as
well as prolonging blood and tissue retention of the compounds. Moreover, the disulfide linkage
in the conjugate is quite labile in the cells or in vivo and thus facilitates intracellular or
extracellular release of the intact compounds from the fatty acid moieties. Reagents and methods
for preparation of the fatty acid derivatives are also provided.

DEPR:
Pursuant to another aspect of the present invention, methods for increasing the absorption or
prolonging blood and tissue retention in a mammal of a sulfhydryl-containing compound of the
general formula PSH are provided, in which a conjugate of general formula VI is formed from the
sulfhydryl-containing compound and the conjugate is then administered to the mammal (for example,
as part of a pharmaceutical composition, e.g. in an aqueous solution or an oral dosage unit)
wherein the conjugate is administered in an amount effective to achieve its intended purpose.

DEPR:
Pursuant to another aspect of the present invention, there are provided methods for increasing
the absorption or prolonging blood and tissue retention in an animal, such as a mammal of a
conjugate (X) which is administered to the animal as part of a pharmaceutical composition (for
example, in an aqueous solution or an oral dosage form).

DEPR:
The fatty acid conjugates of the present invention are soluble in most buffer solutions in which
proteins and peptides are soluble. In particular, any free carboxylic acid groups are charged at
neutral pH and therefore improve the solubility of the conjugates. This greatly facilitates the
formulation of the conjugates with suitable pharmaceutically-acceptable carriers or adjuvants for
administration of the proteins or peptides to a patient by oral or other routes.

DEPR:
The pharmaceutical compositions of the present invention may be administered by any means that
achieve their intended purpose. For example, administration may be by oral, parenteral,
subcutaneous, intravenous, intramuscular, intra-peritoneal, transdermal, intrathecal or
intracranial routes. The dosage administered will be dependent upon the age, health, and weight
of the recipient, kind of concurrent treatment, if any, frequency of treatment, and the nature of
the effect desired.

DEPR:
CT and CT-P were orally administered to CF mice using a gavaging needle at a dose of 100 .mu.g/kg
in PBS. The mice, three of each group, were sacrificed 1 hour after the treatment, and the plasma
was isolated from their blood. The levels of CT and calcium were measured by using commercial
CT-RIA (Phoenix) and calcium diagnostic (Sigma Chemical Co.) kits, respectively. The results are
shown in Table 5. The level of RIA-detected CT in mice with oral administration of CT-P was
significantly higher than that of CT. Furthermore, the level of calcium in plasma at 1 hour was
lower in CT-P treated mice than that in CT treated mice, which was consistent with the finding in
CT levels. Because the crossreactivity of CT-P to the anti-CT antibody is only about 10%, the
actual concentration of total CT in the plasma of CT-P treated mice could be even higher than the
value presented in Table 5.

DEPR:
Liposomal DP-P, as well as DP-P in Tris.RTM. buffer, was tested for its ani-diuretic effects at
an oral dose of 37.5 .mu.g/kg in Brattleboro rats. To prepare liposomal DP-P, a metholic solution
of dimyristoyl phosphatidyl choline, cholesterol and stearylamine (7:2:1) was evaporated to
obtain a dry film. The film was hydrated in Tris.RTM. buffer (2 ml) containing appropriate amount
of DP-P (2 hrs/25.degree. C.), followed by probe sonication (15 min/37.degree. C.). The resultant
liposomal preparation was diluted with Tris.RTM. buffer to a total volume of 5 ml, which was used
immediately. In rats treated with DP-P solution, the total volume of urine collected for the
first five hours after oral administration was 53.3.+-.15.3 ml, which was not significantly
different from that of the control group (47.0.+-.3.5 ml). However, liposomal DP-P showed a
significant anti-diuretic effect with a total urine volume of 27.0.+-.1.0 ml collected for the
first five hours.

DETL:
TABLE 5 _____ Plasma Calcitonin Concentrations and Calcium
Reductions in Mice One Hour after the Oral Administration of CT and CT-P at a Dose of 100
.mu.g/kg (N = 3, "S.D.) CT (pg/0.1 ml plasma) Calcium (% reduction)
_____ CT 9.2 .+-. 0.7 17.5 .+-. 3.6 CT-P 18.3 .+-. 4.0 28.9 .+-.
1.2 _____

ORPL:
Smith, P. et al., "Oral absorption of peptides and proteins," Adv. Drug Delivery Rev.
8(2,3):253-290 (1992).

13. Document ID: US 6083721 A

L10: Entry 13 of 42

File: USPT

Jul 4, 2000

US-PAT-NO: 6083721
DOCUMENT-IDENTIFIER: US 6083721 A
TITLE: Isolated nucleic acid molecules encoding PARG, a GTPase activating protein which interacts
with PTPL1
DATE-ISSUED: July 4, 2000

US-CL-CURRENT: 435/69.1; 435/243, 435/320.1, 435/325, 435/410, 435/91.1, 536/23.1, 536/23.5,
536/24.31, 536/24.33

APPL-NO: 9/ 080855
DATE FILED: May 18, 1998

PARENT-CASE:
This application is a continuation-in-part of U.S. application Ser. No. 08/805,583, filed Feb.
25, 1997.

IN: Saras; Jan, Franzen; Petra, Aspenstrom; Pontus, Hellman; Ulf, Gonez; Leonel
Jorge, Heldin; Carl-Henrik

AB: The invention describes nucleic acids encoding the PARG protein, including
fragments and biologically functional variants thereof. Also included are polypeptides and
fragments thereof encoded by such nucleic acids, and antibodies relating thereto. Methods
and products for using such nucleic acids and polypeptides also are provided.

L10: Entry 13 of 42

File: USPT

Jul 4, 2000

DOCUMENT-IDENTIFIER: US 6083721 A
TITLE: Isolated nucleic acid molecules encoding PARG, a GTPase activating protein which interacts
with PTPL1

DEPR:
The therapeutics of the invention can be administered by any conventional route, including
injection or by gradual infusion over time. The administration may, for example, be oral,

intravenous, intraperitoneal, intramuscular, intracavity, subcutaneous, or transdermal. When
antibodies are used therapeutically, a preferred route of administration is by pulmonary aerosol.
Techniques for preparing aerosol delivery systems containing antibodies are well known to those
of skill in the art. Generally, such systems should utilize components which will not
significantly impair the biological properties of the antibodies, such as the paratope binding
capacity (see, for example, Sciarra and Cutie, "Aerosols," in Remington's Pharmaceutical
Sciences, 18th edition, 1990, pp 1694-1712; incorporated by reference). Those of skill in the art
can readily determine the various parameters and conditions for producing antibody aerosols
without resort to undue experimentation. When using antisense preparations of the invention, slow
intravenous administration is preferred.

DEPR:
The assay mixture also comprises a candidate pharmacological agent. Typically, a plurality of
assay mixtures are run in parallel with different agent concentrations to obtain a different
response to the various concentrations. Typically, one of these concentrations serves as a
negative control, i.e., at zero concentration of agent or at a concentration of agent below the
limits of assay detection. Candidate agents encompass numerous chemical classes, although
typically they are organic compounds. Preferably, the candidate pharmacological agents are small
organic compounds, i.e., those having a molecular weight of more than 50 yet less than about
2500, preferably less than about 1000 and, more preferably, less than about 500. Candidate agents
comprise functional chemical groups necessary for structural interactions with polypeptides
and/or nucleic acids, and typically include at least an amine, carbonyl, hydroxyl or carboxyl
group, preferably at least two of the functional chemical groups and more preferably at least
three of the functional chemical groups. The candidate agents can comprise cyclic carbon or
heterocyclic structure and/or aromatic or polyaromatic structures substituted with one or more of
the above-identified functional groups. Candidate agents also can be biomolecules such as
peptides, saccharides, fatty acids, sterols, isoprenoids, purines, pyrimidines, derivatives or
structural analogs of the above, or combinations thereof and the like. Where the agent is a
nucleic acid, the agent typically is a DNA or RNA molecule, although modified nucleic acids as
defined herein are also contemplated.

DEPR:
to particular cells. In such instances, a vehicle used for delivering a nucleic acid of the
invention into a cell (e.g., a retrovirus, or other virus; a liposome) can have a targeting
molecule attached thereto. For example, a molecule such as an antibody specific for a surface
membrane protein on the target cell or a ligand for a receptor on the target cell can be bound to
or incorporated within the nucleic acid delivery vehicle. For example, where liposomes are
employed to deliver the nucleic acids of the invention, proteins which bind to a surface membrane
protein associated with endocytosis may be incorporated into the liposome formulation for
targeting and/or to facilitate uptake. Such proteins include capsid proteins or fragments thereof
tropic for a particular cell type, antibodies for proteins which undergo internalization in
cycling, proteins that target intracellular localization and enhance intracellular half life, and
the like. Polymeric delivery systems also have been used successfully to deliver nucleic acids
into cells, as is known by those skilled in the art. Such systems even permit oral delivery of
nucleic acids.

14. Document ID: US 6080910 A

L10: Entry 14 of 42

File: USPT

Jun 27, 2000

US-PAT-NO: 6080910
DOCUMENT-IDENTIFIER: US 6080910 A
TITLE: Transgenic knockout animals lacking IgG3
DATE-ISSUED: June 27, 2000

US-CL-CURRENT: 800/18; 800/13, 800/21, 800/3

APPL-NO: 8/ 803120
DATE FILED: February 20, 1997

IN: Schreiber; John R., Greenspan; Neil S., Threadgill; Deborah S., Magnuson; Terry

AB: The present invention provides non-human transgenic animals in which an antibody
subtype is selectively inactivated such that the transgenic animals express a reduced level
of IgG3 relative to the levels expressed by the corresponding wild-type animal. Selective
inactivation is achieved by the disruption through homologous recombination of the a nucleic
acid sequence which encodes a constant region in the antibody subtype. The present invention
provides transgenic animals which contain a disrupted C.gamma.3 gene. These transgenic
animals retain the ability to express other antibody isotypes and subtypes. The present
invention further provides methods for using these transgenic animals for screening
candidate therapeutic compounds and for producing monoclonal antibodies which contain
reduced levels of IgG3.

L10: Entry 14 of 42

File: USPT

Jun 27, 2000

DOCUMENT-IDENTIFIER: US 6080910 A
TITLE: Transgenic knockout animals lacking IgG3

BSPR:
The treatment of SLE in general, and the associated renal dysfunction in particular, focuses on
the alleviation of the general symptoms of the disease using one or a combination of two
modalities, i.e., non-pharmacological treatment and pharmacological treatment.
Non-pharmacological treatment includes periods of bed rest, avoiding exposure to sunlight,
avoiding oral contraceptives and intrauterine devices, and long-term hemodialysis and kidney
transplantation for the treatment of end-stage renal disease. Non-pharmacological treatment is
often used as an adjunct to pharmacological treatment.

DEPR:
The "non-human animals" of the invention comprise any non-human animal whose genome contains an
oligonucleotide sequence (e.g., a gene) encoding a modified form of IgG3. The modification
renders the animal incapable of expressing IgG3 as detected, for example, by Western blot
analysis and Enzyme-Linked Immunosorbent Assay (ELISA). Such non-human animals include
vertebrates such as rodents, non-human primates, ovines, bovines, ruminants, lagomorphs,
porcines, caprines, equines, canines, felines, aves, etc. Preferred non-human animals are
selected from the order Rodentia which includes murines (e.g., rats and mice), most preferably
mice.

DEPR:
A compound is said to be "in a form suitable for administration" when the compound may be
administered to an animal by any desired route (e.g., oral, intravenous, subcutaneous,
intramuscular, etc.) and the compound or its active metabolites appear in the desired cells,
tissue or organ of the animal in an active form.

DEPR:
Candidate antibacterial vaccines are administered to homozygous (.gamma.3 -/-) IgG3-KO transgenic
animals of the present invention and to control wild-type (.gamma.3 +/+) animals. It is preferred
that the transgenic and wild-type animals have an isogenic background in order to minimize
variation in the animals' response. The compounds being tested may be administered using any
suitable route (e.g., oral, parenteral, rectal, controlled-release transdermal patches and
implants, etc.). Generally speaking, the route of administration will depend on the stability of
the compound, the susceptibility of the compound to "first pass" metabolism, the concentration
needed to achieve a therapeutic effect, and the like. As is clearly demonstrated herein, the
transgenic animals of the present invention, while producing substantially reduced levels of IgG3
relative to wild-type levels, are still capable of expressing other antibodies, e.g., IgM and
IgG2b. Using this information, one of skill in the art may initially screen the ability of the
candidate compound to induce the production of IgG subtypes other than IgG3, as well as isotypes
other than IgG. A given compound's relative efficacy as an antibacterial vaccine in relation to
other candidate compounds may be determined based on (1) the total level of immunoglobulins
produced, (2) the level of one or more selected antibody isotype or subtype, or (3) functional
assays, e.g., facilitation of phagocytosis and killing by neutrophils or monocytes. Methods for
the determination of antibody isotypes and subtypes are provided herein in Example 1.

15. Document ID: US 6066778 A

L10: Entry 15 of 42

File: USPT

May 23, 2000

US-PAT-NO: 6066778
DOCUMENT-IDENTIFIER: US 6066778 A
TITLE: Transgenic mice expressing APC resistant factor V

DATE-ISSUED: May 23, 2000

US-CL-CURRENT: 800/3; 424/9.2, 800/18, 800/22, 800/25, 800/9

APPL-NO: 8/ 746111
DATE FILED: November 6, 1996

IN: Ginsburg; David, Cui; Jisong

AB: The present invention relates to compositions and methods for the screening of
compounds for anticoagulant activity. In particular, the present invention relates to
non-human transgenic animals expressing activated protein C ("APC")-resistant factor V
proteins which display a predisposition toward spontaneous thrombosis. The present invention
also provides methods for using these transgenic animals to screen compounds for
anticoagulant activity.

L10: Entry 15 of 42

File: USPT

May 23, 2000

DOCUMENT-IDENTIFIER: US 6066778 A
TITLE: Transgenic mice expressing APC resistant factor V

BSPR:
The most frequently observed untoward effect of the coumarin and indandione agents is hemorrhage;
as with heparin, this is actually an extension of the agents' pharmacological effect. Indeed,
minor incidents of bleeding occur in approximately 1% of patients receiving these agents per year
of therapy. Though not as common, massive hemorrhage can also occur with oral anticoagulant
treatment, most frequently in the gastrointestinal tract or genitourinary region. In addition to
having a relatively narrow therapeutic index, coumarin is a teratogen and cannot be administered
to pregnant patients.

BSPR:
fact that hemorrhage may occur when the prothrombin time is in the normal range (often due, e.g.,
when occult lesions are present). Moreover, many commonly used pharmaceutical agents (e.g.,
metronidazole, barbiturates, and oral contraceptives) may increase or decrease the patient's
response to oral anticoagulant agents, especially warfarin, necessitating close monitoring of
which medications are being taken and adjusting the dose of the anticoagulant agent when
appropriate. [See generally, AHFS Drug Information, Gerald K. McKevoy, ed., pp. 924-29 (1995)].

BSPR:
The present invention further provides a method for screening compounds for anticoagulant
activity, comprising: a) providing: i) a non-human animal expressing an APC resistant factor V;
ii) a composition comprising a test compound in a form suitable for administration such that the
compound is bioavailable in the blood of the animal; and b) administering the test compound to
the non-human animal. In one embodiment, the method further comprises c) measuring a reduction in
the incidence of microvascular thrombi and thereby identifying a compound as therapeutic. The
present invention is not limited by the nature of the compound to be screened for anticoagulant
activity. In a preferred embodiment, the test compound is selected from the group consisting of

heparin, oral anticoagulants (e.g., 4-hydroxycoumarin, dicumarol, phenprocoumon, warfarin sodium and indanedione derivatives), antithrombotics or anti-platelet drugs (i.e., drugs which suppress platelet function such as aspirin, sulfinpyrazone, dipyridamole, dextran 70, dextran 75, dazoxiben, ticlopidine and clofibrate), fibrinolytics or thrombolytics (i.e., drugs which promote the dissolution of thrombi by stimulating the activation of plasminogen to plasmin such as streptokinase, urokinase, tissue-type plasminogen activator, urokinase-type plasminogen activator, and aminocaproic acid). In addition, compounds which have been reported or proposed to protect or speed the healing of infarcted tissue such as growth factors and anti-oxidants many be tested for anticoagulation activity in the methods of the present invention.

DEPR:
The "non-human animals" of the invention comprise any non-human animal whose genome contains an oligonucleotide sequence (e.g., a gene) encoding a modified form of factor V (FV). The modification may render the resulting factor V protein resistant to the natural anticoagulant action of activated protein C (APC) (referred to as an "APC resistant factor V" protein) or may render the resulting factor V protein completely nonfunctional. Such non-human animals include vertebrates such as rodents, non-human primates, ovines, bovines, ruminants, lagomorphs, porcines, caprines, equines, canines, felines, aves, etc. Preferred non-human animals are selected from the order Rodentia which includes murines (e.g., rats and mice), most preferably mice.

DEPR:
A compound is said to be "in a form suitable for administration such that the compound is bioavailable in the blood of the animal" when the compound may be administered to an animal by any desired route (e.g., oral, intravenous, subcutaneous, intramuscular, etc.) and the compound or its active metabolites appears in the blood of the animal in an active form. Administration of a compound to a pregnant female may result in delivery of bioavailable compound to the fetuses of the pregnant animal.

DEPR:
The transgenic mice of the present invention which express APC resistant FV proteins provide animal models for human thrombophilia and provide a means to screen compounds for anticoagulant activity. As described in detail herein, transgenic animals expressing APC resistant FV proteins display spontaneous thrombosis. With regarding to transgenic animals homozygous for the R504Q mutation, approximately one-third to one-half of these homozygous mice die within the immediate postnatal period. Using that information, a screening method is performed utilizing a non-transgenic control group and a transgenic treatment group. Compounds to be tested for anticoagulant activity are administered to the same number of pregnant mice (generated using R504Q homozygote crosses) from the control group and the treatment group, and the survival of the pups used as a measure of efficacy. The compounds being tested can be administered using any suitable route (e.g., oral, parenteral, rectal, controlled-release transdermal patches and implants, etc.). Generally speaking, the route of administration will depend on the stability of the compound, the susceptibility of the compound to "first pass" metabolism, the concentration needed to achieve a therapeutic effect, and the like. Following initial screening, a compound that appears promising (i.e., which increases the number of pups which survive the imme diate postnatal period relative to the untreated control group) is further evaluated by administering various concentrations of the compound to transgenic animals in order to determine an approximate therapeutic dosing range.

CLPR:
10. The method of claim 9, wherein said test compound is selected from the group consisting of heparin, oral anticoagulants, antithrombotics, and thrombolytics.

16. Document ID: US 6060590 A

L10: Entry 16 of 42

File: USPT

May 9, 2000

US-PAT-NO: 6060590
DOCUMENT-IDENTIFIER: US 6060590 A
TITLE: Chitinase related proteins and methods of use
DATE-ISSUED: May 9, 2000

US-CL-CURRENT: 530/399; 530/350

APPL-NO: 9/ 052778
DATE FILED: March 31, 1998

IN: Bryant; Peter J., Kawamura; Kazuo

AB: A family of chitinase related proteins (CHRPs) that promote cell growth and may be useful in wound healing and other indications is provided. In a particular embodiment, imaginal disc growth factor 4 (IDGF4) protein and polynucleotides encoding the protein are provided. The IDGF polypeptides of the family promote cell growth when added exogenously to imaginal disc cell lines. Methods of use for members of the CHRP family, including IDGF1, IDGF2, IDGF3, IDGF4, DS47, gp38k, gp-39, Brp-39, YKL39, YKL40, POSP and homologs or orthologs thereof, are included for accelerating wound healing and tissue growth, modulating angiogenesis and ameliorating cell proliferative disorders in human patients.

L10: Entry 16 of 42

File: USPT

May 9, 2000

DOCUMENT-IDENTIFIER: US 6060590 A
TITLE: Chitinase related proteins and methods of use

DEPR:
The CHRP protein or antibody can be administered parenterally by injection, rapid infusion, nasopharyngeal absorption, dermal absorption, and orally. Pharmaceutically acceptable carrier preparations for parenteral administration include sterile or aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate.

Carriers for occlusive dressings can be used to increase skin permeability and enhance antigen absorption. Liquid dosage forms for oral administration may generally comprise a liposome solution containing the liquid dosage form. Suitable solid or liquid pharmaceutical preparation forms are, for example, granules, powders, tablets, coated tablets, (micro)capsules, suppositories, syrups, emulsions, suspensions, creams, aerosols, drops or injectable solution in ampule form and also preparations with protracted release of active compounds, in whose preparation excipients and additives and/or auxiliaries such as disintegrants, binders, coating agents, swelling agents, lubricants, flavorings, sweeteners and elixirs containing inert diluents commonly used in the art, such as purified water.

DEPR:
Candidate agents encompass numerous chemical classes, though typically they are organic molecules, preferably small organic compounds having a molecular weight of more than 50 and less than about 2,500 daltons. Candidate agents comprise functional groups necessary for structural interaction with proteins, particularly hydrogen bonding, and typically include at least an amine, carbonyl, hydroxyl or carboxyl group, preferably at least two of the functional chemical groups. The candidate agents often comprise cyclical carbon or heterocyclic structures and/or aromatic or polyaromatic structures substituted with one or more of the above finctional groups.
Candidate agents are also found among biomolecules including, but not limited to: peptides, saccharides, fatty acids, steroids, purines, pyrimidines, derivatives, structural analogs or combinations thereof. Candidate agents are obtained from a wide variety of sources including libraries of synthetic or natural compounds. For example, numerous means are available for random and directed synthesis of a wide variety of organic compounds and biomolecules, including expression of randomized oligonucleotides and oligopeptides. Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant and animal extracts are available or readily produced. Additionally, natural or synthetically produced libraries and compounds are readily modified through conventional chemical, physical and biochemical means, and may be used to produce combinatorial libraries. Known pharmacological agents may be subjected to directed or random chemical modifications, such as acylation, alkylation, esterification and amidification to produce structural analogs.

17. Document ID: US 6051374 A

L10: Entry 17 of 42

File: USPT

Apr 18, 2000

US-PAT-NO: 6051374
DOCUMENT-IDENTIFIER: US 6051374 A
TITLE: Non-A, non-B, non-C, non-D, non-E hepatitis reagents and methods for their use
DATE-ISSUED: April 18, 2000

US-CL-CURRENT: 435/5; 435/6, 435/810, 435/91.2, 435/91.52, 536/23.1, 536/24.32

APPL-NO: 8/ 488445
DATE FILED: June 7, 1995

PARENT-CASE:
This application is a continuation-in-part application of U.S. Ser. No. 08/377,557 filed Jan. 30, 1995, which is a continuation-in-part of U.S. Ser. No. 08/344,185 filed Nov. 23, 1994 and U.S. Ser. No. 08/344,190 filed Nov. 23, 1994, which are each continuation-in-part applications of Ser. No. 08/283,314 filed Jul. 29, 1994, which is a continuation-in-part application of U.S. Ser. No. 08/242,654, filed May 13, 1994, which is a continuation-in-part application of U.S. Ser. No. 08/196,030 filed Feb. 14, 1994, all of which are abandoned, all of which enjoy common ownership and each of which is incorporated herein by reference.

IN: Simons; John N., Pilot-Matias; Tami J., Dawson; George J., Schlauder; George G., Desai; Suresh M., Leary; Thomas P., Muerhoff; Anthony Scott, Erker; James Carl, Buijk; Sheri L., Mushahwar; Isa K.

AB: Hepatitis GB Virus (HGBV) nucleic acid and amino acid sequences useful for a variety of diagnostic and therapeutic applications, kits for using the HGBV nucleic acid or amino acid sequences, HGBV immunogenic particles, and antibodies which specifically bind to HGBV. Also provided are methods for producing antibodies, polyclonal or monoclonal, from the HGBV nucleic acid or amino acid sequences.

L10: Entry 17 of 42

File: USPT

Apr 18, 2000

DOCUMENT-IDENTIFIER: US 6051374 A
TITLE: Non-A, non-B, non-C, non-D, non-E hepatitis reagents and methods for their use

DEPR:
The RDA procedure as described supra is a modification of the representational difference analysis known in the art. The method was modified to isolate viral clones from pre-inoculation and infectious sera sources. These modifications are discussed further below and relate to the preparation of amplicons for both tester and driver DNA. First, the starting material was not double-stranded DNA obtained from the genomic DNA of mammalian cells as reported previously, but total nucleic acid extracted from infectious and pre-inoculation biological blood samples obtained from tamarins. It is possible that other biological samples (for example, organs, tissue, bile, feces or urine) could be used as sources of nucleic acid from which tester and driver amplicons are generated. Second, the amount of starting nucleic acid is substantially less than that described in the art. Third, a restriction endonuclease with a 4 bp instead of a 6 bp recognition site was used. This is substantially different from the prior art. Lisitsyn et al. teach that RDA works because the generation of amplicons (i.e. representations) decreases the complexity of the DNA that is being hybridized (i.e. subtracted).

DEPR:
The vaccines usually are administered by intravenous or intramuscular injection. Additional formulations which are suitable for other modes of administration include suppositories and, in

some cases, oral formulations. For suppositories, traditional binders and carriers may include
but are not limited to polyalkylene glycols or triglycerides. Such suppositories may be formed
from mixtures containing the active ingredient in the range of about 0.5% to about 10%,
preferably, about 1% to about 2%. Oral formulation include such normally employed excipients as,
for example pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium
saccharine, cellulose, magnesium carbonate and the like. These compositions may take the form of
solutions, suspensions, tablets, pills, capsules, sustained release formulations or powders and
contain about 10% to about 95% of active ingredient, preferably about 25% to about 70%.

18. Document ID: US 6020330 A

L10: Entry 18 of 42

File: USPT

Feb 1, 2000

US-PAT-NO: 6020330
DOCUMENT-IDENTIFIER: US 6020330 A
TITLE: Hypolipidemic 1,4-benzothiazepine-1,1-dioxides
DATE-ISSUED: February 1, 2000

US-CL-CURRENT: 514/43; 514/211.09, 514/27, 536/17.4, 540/552

APPL-NO: 9/041953
DATE FILED: March 13, 1998

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
EP	97104348	March 14, 1997

IN: Enhsen; Alfons, Falk; Eugen, Glombik; Heiner, Stengelin; Siegfried

AB: The present invention is concerned with new hypolipidemic compounds, with
processes and novel intermediates for their preparation, with pharmaceutical compositions
containing them and with their use in medicine, particularly in the prophylaxis and
treatment of hyperlipidemic conditions, such as atherosclerosis., Compounds of the formula
(I): ##STR1## wherein R.sup.1 to R.sup.10 and X are a defined in the specification and are
useful as hypolipidemic compounds.

L10: Entry 18 of 42

File: USPT

Feb 1, 2000

DOCUMENT-IDENTIFIER: US 6020330 A
TITLE: Hypolipidemic 1,4-benzothiazepine-1,1-dioxides

BSPR:
Pharmaceutical compositions according to the present invention include those suitable for oral,
rectal, topical, buccal (e.g. sub-lingual) and parenteral (e.g. subcutaneous, intramuscular,
intradermal, or intravenous) administration, although the most suitable route in any given case
will depend on the nature and severity of the condition being treated and on the nature of the
particular compound of formula (I) which is being used. Enteric-coated and enteric-coated
controlled release formulations are also within the scope of the invention. Preferred are acid
and gastric juice resistant formulations. Suitable enteric coatings include cellulose acetate
phthalate, polyvinylacetate phthalate, hydroxypropylmethylcellulose phthalate and anionic
polymers of methacrylic acid and methacrylic acid methyl ester.

BSPR:
Pharmaceutical compositions suitable for oral administration can be presented in discrete units,
such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of a
compound of formula (I); as a powder or granules; as a solution or a suspension in an aqueous or
non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. As indicated, such
compositions can be prepared by any suitable method of pharmacy which includes the step of
bringing into association the active compound and the carrier (which can constitute one or more
accessory ingredients). In general, the compositions are prepared by uniformly and intimately
admixing the active compound with a liquid or finely divided solid carrier, or both, and then, if
necessary, shaping the product. For example, a tablet can be prepared by compressing or moulding
a powder or granules of the compound, optionally with one or more accessory ingredients.
Compressed tablets can be prepared by compressing, in a suitable machine, the compound in a
free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert
diluent and/or surface active/dispersing agent(s). Moulded tablets can be made by moulding, in a
suitable machine, the powdered compound moistened with an inert liquid diluent.

BSPR:
Pharmaceutical compositions suitable for rectal administration are preferably presented as
unit-dose suppositories. These can be prepared by admixing a compound of formula (I) with one or
more conventional solid carriers, for example, cocoa butter, and then shaping the resulting
mixture.

BSPR:
In order to prove the greater hypolipidemic activity of the compounds according to the invention
tests were carried out by means of three genetically modified cell lines. These were derivatives
of the generally known "Chinese hamster ovary" (CHO) cell line, which on account of incorporated
expression plasmids additionally produced sodium-dependent bile acid transporters. The first cell
line (CHO/pRIBAT8) was in this case the ileal transporter of the rabbit (RIBAT), the second
(CHO/pHIBAT8) the ileal transporter of the human (HIBAT) and the third (CHO/pHLBAT5) the hepatic
transporter of the human. All plasmids were based on the standard plasmid pCDNA1neo, which as
important elements has a cytomegaloviral promoter for the permanent expression of heterologous
genes and a gene for the production of cell resistance against the substance G418.

BSPR:
For the preparation of the genetically modified cell lines, CHO cells were transfected with DNA

from pRIBAT8, pHIBAT8 or pHLBAT5 and cells which developed resistance against the selection substance G418 were selectively additionally cultured by addition of the substance to the cell medium. The cells CHO/pRIBAT8, CHO/pHIBAT8 and CHO/pHLBAT5 were then isolated from the amount of G418-resistant cells and pure clonal lines were cultured therefrom. The tool used for following the isolation process was in this case a fluorescent bile acid derivative (3.beta.-NBD-NCT; N-[7-(4-nitrobenzo-2-oxa-1,3-diazol)]-3.beta.-amino-7a, 12a-dihydroxy -5.beta.-cholan-24-oyl)-2'-aminoethanesulfonate. Cells with intact bile acid transporters rapidly absorbed this substance from the cell medium and as a result became fluorescent. They could thereby be easily differentiated from cells without intact bile acid transporters with the aid of a fluorescence microscope.

19. Document ID: US 5998596 A

L10: Entry 19 of 42

File: USPT

Dec 7, 1999

US-PAT-NO: 5998596
DOCUMENT-IDENTIFIER: US 5998596 A
TITLE: Inhibition of protein kinase activity by aptameric action of oligonucleotides
DATE-ISSUED: December 7, 1999

US-CL-CURRENT: 536/22.1; 536/23.1, 536/24.3

APPL-NO: 8/ 416214
DATE FILED: April 4, 1995

IN: Bergan; Raymond, Neckers; Len

AB: The present invention are oligonucleotides that specifically bind to and directly inhibit the biological function of target molecules such as proteins, peptides or derivatives. The direct or aptameric interaction of oligonucleotides of the present invention with proteins, peptides and derivatives represents a non-antisense mediated effect. The oligonucleotides have been shown to bind to isolated target molecules and to inhibit biological function of the target molecule within cells. In particular, the oligonucleotides have been shown to directly inhibit the kinase activity of protein-tyrosine kinase. The oligonucleotides of the present invention have significant beneficial effects against a chronic myelogenous leukemia derived cell line as demonstrated using cellular phosphotyrosine content as well as cellular growth in soft agar.

L10: Entry 19 of 42

File: USPT

Dec 7, 1999

DOCUMENT-IDENTIFIER: US 5998596 A
TITLE: Inhibition of protein kinase activity by aptameric action of oligonucleotides

DEPR:

The oligonucleotides of the present invention may be also modified by the addition of groups to facilitate their entry into cells. Such groups include but are not limited to non-polypeptide polymers, polypeptides, lipophilic groups and the like. "Lipophilic" groups refer to moieties which are chemically compatible with the outer cell surface, i.e., so as to enable the oligonucleotide to attach to, merge with and cross the cell membrane. Examples of such lipophilic groups are fatty acids and fatty alcohols in addition to long chain hydrocarbyl groups. Such modified oligonucleotides and methods for making the oligonucleotides are disclosed in U.S. Pat. No. 5,256,775.

DEPR:

Administration may also be by transmucosal or transdermal means, or the compounds may be administered orally. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated as used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration bile salts and fusidic acid derivatives. In addition, detergents may be used to facilitate permeation. Transmucosal administration may be through nasal sprays, for example, or using suppositories. For oral administration, the oligonucleotides are formulated into conventional oral administration forms such as capsules, tablets, and tonics.

20. Document ID: US 5994062 A

L10: Entry 20 of 42

File: USPT

Nov 30, 1999

US-PAT-NO: 5994062
DOCUMENT-IDENTIFIER: US 5994062 A
TITLE: Epithelial protein and DNA thereof for use in early cancer detection
DATE-ISSUED: November 30, 1999

US-CL-CURRENT: 435/6; 435/91.2, 435/91.21, 536/23.5, 536/24.32, 536/24.33

APPL-NO: 8/ 538711
DATE FILED: October 2, 1995

IN: Mulshine; James L., Tockman; Melvyn S.

AB: The present invention is a purified and isolated epithelial protein, peptide and variants thereof whose increased presence in an epithelial cell is at indicative of precancer. One epithelial protein which is an early detection marked for lung cancer was purified from two human lung cancer cell lines, NCI-H720 and NCI-H157. Using a six-step procedure, the epithelial protein was purified using a Western blot detection system under both non-reducing and reducing conditions. Purification steps included anion exchange chromatography, preparative isoelectric focusing, polymer-based C.sub.18 HPLC and analytic C.sub.4 HPLC. After an approximately 25,000 fold purification the immunostaining protein was >90% pure as judged by coomassie blue staining after reducing

SDS-PAGE. The primary
epithelial protein share some sequence homology with the heterogeneous nuclear
ribonucleoprotein (hnRNP) A2. A minor co-purifying epithelial protein shares some sequence
homology with the splice variant hnRNP-B1. Molecular analysis of primary normal bronchial
epithelial cell cultures demonstrated a low level the epithelial protein expression,
consistent with immunohistochemical staining of clinical samples, and an increased level of
expression in most lung cancer cells. The epithelial protein is a marker of epithelial
transformation in lung, breast, bone, ovary, prostate, kidney, melanoma and myeloma and may
be casual in the process of carcinogenesis. Methods are provided for monitoring the
expression of the epithelial protein, peptides and variants using molecular and
immunological techniques as a screen for precancer and cancer in mammals.

L10: Entry 20 of 42

File: USPT

Nov 30, 1999

DOCUMENT-IDENTIFIER: US 5994062 A
TITLE: Epithelial protein and DNA thereof for use in early cancer detection

DEPR:
The oligonucleotides of the present invention may also be modified by the addition of groups to
facilitate their entry into cells. Such groups include but are not limited to, non-polypeptide
polymers, polypeptides, lipophilic groups and the like. Lipophilic groups refer to moieties which
are chemically compatible with the outer cell surface, i.e., so as to enable the oligonucleotide
to attach to, merge with and cross the cell membrane. Examples of such lipophilic groups are
fatty acids and fatty alcohols, in addition to long chain hydrocarbyl groups. Such modified
oligonucleotides and methods for making are disclosed in U.S. Pat. No. 5,256,775.

DEPR:
The route of administration may be intravenous, intramuscular, subcutaneous, intradermal,
intraperitoneal, intrathecal, ex vivo, and the like. Administration may also be by transmucosal
or transdermal means, or the compound may be administered orally. For transmucosal or transdermal
administration, penetrants appropriate to the barrier to be permeated as used in the formulation.
Such penetrants are generally known in the art, and include, for example, for transmucosal
administration bile salts and fusidic acid derivatives. In addition, detergents may be used to
facilitate permeation. Transmucosal administration may be through nasal sprays, for example, or
using suppositories. For oral administration, the oligonucleotides are formulated into
conventional oral administration forms, such as capsules, tablets and tonics. For topical
administration, the oligonucleotides of the invention are formulated into ointments, salves,
gels, or creams, as is generally known in the art.

DEPR:
8. Slaughter, D., Southwick, H. and Smejkal, W. "Field cancerization" in oral stratified squamous
epithelium. Cancer, 6: 963-968, 1953.

21. Document ID: US 5981172 A

L10: Entry 21 of 42

File: USPT

Nov 9, 1999

US-PAT-NO: 5981172
DOCUMENT-IDENTIFIER: US 5981172 A
TITLE: Non-A, non-B, non-C, non-D, non-E Hepatitis reagents and methods for their use
DATE-ISSUED: November 9, 1999

US-CL-CURRENT: 435/5; 435/6, 536/23.1, 536/24.3

APPL-NO: 8/417629
DATE FILED: April 6, 1995

PARENT-CASE:
This application is a continuation-in-part application of PCT/US95/02118, filed Feb. 14, 1995,
which is a continuation-in-part application of U.S. Ser. No. 08/377,557 filed Jan. 30, 1995 now
abandoned, which is a continuation-in-part of U.S. Ser. No. 08/344,185 filed Nov. 23, 1994 now
abandoned and U.S. Ser. No. 08/344,190 filed Nov. 23, 1994 now abandoned, which are each
continuation-in-part applications of 08/283,314 filed Jul. 29, 1994, now abandoned, which is a
continuation-in-part application of U.S. Ser. No. 08/242,654, filed May 13, 1994 now abandoned,
which is a continuation-in-part application of U.S. Ser. No. 08/196,030 filed Feb. 14, 1994 now
abandoned, all of which enjoy common ownership and each of which is incorporated herein by
reference.

IN: Simons; John N., Pilot-Matias; Tami J., Dawson; George J., Schlauder; George G.,
Desai; Suresh M., Leary; Thomas P., Muerhoff; Anthony Scott, Buijk; Sheri L., Erker; James
Carl, Mushahwar; Isa K.

AB: Hepatitus GB Virus (HGBV) nucleic acid and amino acid sequences useful for a
variety of diagnostic and theraeutic applications, kits for using the HGBV nucleic acid or
amino acid sequences, HGBV immunogenic particles, and antibodies which specifically bind to
HGBV. Also provided are methods for producing antibodies, polyclonal or monoclonal, from the
HGBV nucleic acid or amino acid sequences.

L10: Entry 21 of 42

File: USPT

Nov 9, 1999

DOCUMENT-IDENTIFIER: US 5981172 A
TITLE: Non-A, non-B, non-C, non-D, non-E Hepatitis reagents and methods for their use

DEPR:
The RDA procedure as described supra is a modification of the representational difference
analysis known in the art. The method was modified to isolate viral clones from pre-inoculation
and infectious sera sources. These modifications are discussed further below and relate to the
preparation of amplicons for both tester and driver DNA. First, the starting

material was not
double-stranded DNA obtained from the genomic DNA of mammalian cells as reported previously, but
total nucleic acid extracted from infectious and pre-inoculation biological blood samples
obtained from tamarins. It is possible that other biological samples (for example, organs,
tissue, bile, feces or urine) could be used as sources of nucleic acid from which tester and
driver amplicons are generated. Second, the amount of starting nucleic acid is substantially less
than that described in the art. Third, a restriction endonuclease with a 4 bp instead of a 6 bp
recognition site was used. This is substantially different from the prior art. Lisitsyn et al.
teach that RDA works because the generation of amplicons (i.e. representations) decreases the
complexity of the DNA that is being hybridized (i.e. subtracted).

DEPR:
The vaccines usually are administered by intravenous or intramuscular injection. Additional
formulations which are suitable for other modes of administration include suppositories and, in
some cases, oral formulations. For suppositories, traditional binders and carriers may include
but are not limited to polyalkylene glycols or triglycerides. Such suppositories may be formed
from mixtures containing the active ingredient in the range of about 0.5% to about 10%,
preferably, about 1% to about 2%. Oral formulation include such normally employed excipients as,
for example pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium
saccharine, cellulose, magnesium carbonate and the like. These compositions may take the form of
solutions, suspensions, tablets, pills, capsules, sustained release formulations or powders and
contain about 10% to about 95% of active ingredient, preferably about 25% to about 70%.

22. Document ID: US 5977309 A

L10: Entry 22 of 42
File: USPT
Nov 2, 1999

US-PAT-NO: 5977309
DOCUMENT-IDENTIFIER: US 5977309 A
TITLE: Cytostatin I
DATE-ISSUED: November 2, 1999

US-CL-CURRENT: 530/350; 435/252.3, 435/320.1, 435/325, 435/471, 435/69.1, 435/71.1, 435/71.2,
536/23.1, 536/23.5, 536/24.3, 536/24.31

APPL-NO: 9/ 023073
DATE FILED: February 13, 1998

PARENT-CASE:
This application is a division of Ser. No. 08/409,731 filed Mar. 24, 1995 now U.S. Pat. No.
5,658,758.

IN: Ni; Jian, Gentz; Reiner, Yu; Guo-Liang, Rosen; Craig A.

AB: A human cytostatin I polypeptide an DNA encoding such polypeptide and a procedure
for producing such polypeptide by recombinant techniques is disclosed. Also disclosed are
methods for utilizing such polypeptide for the treatment of cancers, particularly breast
cancer, leukemias, and other matastases.

L10: Entry 22 of 42
File: USPT
Nov 2, 1999

DOCUMENT-IDENTIFIER: US 5977309 A
TITLE: Cytostatin I

BSPR:
Peptides that locally signal growth cessation and stimulate differentiation of the developing
epithelium are very important for mammary gland development. Recombinant and wild-type forms of
mammary-derived growth inhibitor (MDGI) and heart-fatty acid binding protein (FABP), which belong
to the FABP family, specifically inhibit growth of normal mouse mammary epithelial cells (MEC)
and promote morphological differentiation, stimulates its own expression and promotes milk
protein synthesis. Selective inhibition of endogenous MDGI expression in MEC by antisense
phosphorothioate oligonucleotides suppresses appearance of alveolar end buds and lowers the
beta-casein level in organ cultures. Furthermore, MDGI suppresses the mitogenic effects of EGF,
and EGF antagonizes the activities of MDGI. Finally, the regulatory properties of MDGI can be
fully mimicked by an 11-amino acid sequence, represented in the COOH terminus of MDGI and a
subfamily of structurally related FABPs. MDGI is the first known growth inhibitor which promotes
mammary gland differentiation. The amount of MDGI increased dramatically with the onset of
lactation after delivery. Recent studies shows that a new posttranslational processing form of
MDGI, MDGI 2, not present in lactation, was found in the bovine gland during pregnancy. (Brandt
et al, Biochem Biophy Res Comm Vol 189, p 406, Nov. 30, 1992) To date, bovine, rat and mouse MDGI
have been identified but no human MDGI or MDGI-like protein.

DEPR:
The pharmaceutical compositions may be administered in a convenient manner such as by the oral
(when protected from hydrolysis or digestion), topical, intravenous, intraperitoneal,
intramuscular, subcutaneous, intranasal or intradermal routes. The pharmaceutical compositions
are administered in an amount which is effective for treating and/or prophylaxis of the specific
indication. In general, they are administered in an amount of at least about 10 .mu.g/kg body
weight and in most cases they will be administered in an amount not in excess of about 8 mg/Kg
body weight per day. In most cases, the dosage is from about 10 .mu.g/kg to about 1 mg/kg body
weight daily, taking into account the routes of administration, symptoms, etc.

23. Document ID: US 5968909 A

L10: Entry 23 of 42
File: USPT
Oct 19, 1999

US-PAT-NO: 5968909
DOCUMENT-IDENTIFIER: US 5968909 A
TITLE: Method of modulating gene expression with reduced immunostimulatory response
DATE-ISSUED: October 19, 1999

US-CL-CURRENT: 514/44; 536/24.5

APPL-NO: 8/ 511536
DATE FILED: August 4, 1995

IN: Agrawal; Sudhir, Temsamani; Jamal, Zhao; Qiuyan

AB: The present invention provides a method of reducing the immunostimulatory effects of certain phosphorothioate oligonucleotides used to treat pathogen-mediated disease states and other medical conditions. Immunostimulatory effects of phosphorothioate oligonucleotides are reduced in accordance with the method of the invention by modifying at least one chemical structure within the phosphorothioate oligonucleotide to produce an immunostimulatory response-reducing phosphorothioate oligonucleotide, which is then administered to a mammal afflicted with the disease or condition being treated. The immune response of the mammal is also monitored in the method of the invention.

L10: Entry 23 of 42
File: USPT
Oct 19, 1999

DOCUMENT-IDENTIFIER: US 5968909 A
TITLE: Method of modulating gene expression with reduced immunostimulatory response

DEPR:
The therapeutic formulation used in the method of the invention may be in the form of a liposome in which the immunostimulatory response-reducing phosphorothioate oligonucleotides of the invention are combined, in addition to other pharmaceutically acceptable carriers, with amphipathic agents such as lipids which exist in aggregated form as micelles, insoluble monolayers, liquid crystals, or lamellar layers which are in aqueous solution. Suitable lipids for liposomal formulation include, without limitation, monoglycerides, diglycerides, sulfatides, lysolecithin, phospholipids, saponin, bile acids, and the like. Preparation of such liposomal formulations is within the level of skill in the art, as disclosed, for example, in U.S. Pat. No. 4,235,871; U.S. Patent No. 4,501,728; U.S. Pat. No. 4,837,028; and U.S. Pat. No. 4,737,323. The therapeutic formulation used in the method of the invention may further include other lipid carriers, such as lipofectamine, or cyclodextrins (Zhao et al. (1995) Antisense Res. Dev. (in press)) and the like, which enhance delivery of oligonucleotides into cells, or such as slow release polymers.

DEPR:
Administration of the immunostimulatory response-reducing phosphorothioate oligonucleotide in accordance with the method of the invention can be carried out in a variety of conventional ways, such as oral ingestion, inhalation, or cutaneous, subcutaneous, intramuscular, or intravenous injection.

24. Document ID: US 5936092 A

L10: Entry 24 of 42
File: USPT
Aug 10, 1999

US-PAT-NO: 5936092
DOCUMENT-IDENTIFIER: US 5936092 A
TITLE: Methods and compositions for lipidization of hydrophilic molecules
DATE-ISSUED: August 10, 1999

US-CL-CURRENT: 546/294; 552/544, 552/548, 562/431

APPL-NO: 8/ 742357
DATE FILED: November 1, 1996

PARENT-CASE:
This application is a division of application Ser. No. 08/524,362 filed on Sep. 5, 1995 which application is now pending, and which is a continuation-in-part of application Ser. No. 08/349,717 filed Jan. 25, 1995, which application is now abandoned.

IN: Shen; Wei-Chiang, Ekrami; Hossein M.

AB: Fatty acid derivatives of sulfhydryl-containing compounds (for example, sulfhydryl-containing peptides or proteins) comprising fatty acid-conjugated products with a disulfide linkage are employed for delivery of the compounds to mammalian cells. This modification markedly increases the absorption of the compounds by mammalian cells relative to the rate of absorption of the unconjugated compounds, as well as prolonging blood and tissue retention of the compounds. Moreover, the disulfide linkage in the conjugate is quite labile in the cells and thus facilitates intracellular release of the intact compounds from the fatty acid moieties.

L10: Entry 24 of 42
File: USPT
Aug 10, 1999

DOCUMENT-IDENTIFIER: US 5936092 A
TITLE: Methods and compositions for lipidization of hydrophilic molecules

BSPR:
Alternative routes of protein and peptide delivery may include the buccal, nasal, oral, pulmonary, rectal and ocular routes. Without exception, these routes are less effective than the parenteral routes of administration. However, these routes of protein and peptide delivery are still far more attractive than the parenteral routes because they offer convenience and control to the patients. The oral route is particularly attractive because it is the most convenient and patient-compliant.

BSPR:
Mucosal barriers, which separate the inside of the body from the outside (e.g. GI, ocular, pulmonary, rectal and nasal mucosa), comprise a layer of tightly joined cell monolayers which

strictly regulates the transport of molecules. Individual cells in barriers are joined by tight
junctions which regulate entry into the intercellular space.

BSPR:
In addition to providing a tight physical barrier to the transport of proteins and peptides,
mucosal barriers possess enzymes which can degrade proteins and peptides before, after, and
during their passage across the mucosa. This barrier is referred to as the enzymatic barrier. The
enzymatic barrier consists of endo- and exopeptidase enzymes which cleave proteins and peptides
at their terminals or within their structure. Enzymatic activity of several mucosa have been
studied and the results demonstrated that substantial protease activity exists in the homogenates
of buccal, nasal, rectal and vaginal mucosa of albino rabbits and that these activities are
comparable to those present in the ilium [Lee et al. (1988), supra]. Therefore, regardless of the
mucosa being considered, the enzymatic barrier present will feature strongly in the degradation
of the protein and peptide molecules.

BSPR:
In accordance with the present invention, fatty acid derivatives of sulfhydryl-containing
compounds (for example, peptides, proteins or oligonucleotides which contain or are modified to
contain sulfhydryl groups) comprising fatty acid-conjugated products with a disulfide linkage are
employed for delivery of the sulfhydryl-containing compounds to mammalian cells. This
modification markedly increases the absorption of the compounds by mammalian cells relative to
the rate of absorption of the unconjugated compounds, as well as prolonging blood and tissue
retention of the compounds. Moreover, the disulfide linkage in the conjugate is quite labile in
the cells and thus facilitates intracellular release of the intact compounds from the fatty acid
moieties. Reagents and methods for preparation of the fatty acid derivatives are also provided.

DEPR:
Pursuant to another aspect of the present invention, methods for increasing the absorption or
prolonging blood and tissue retention in a mammal of a sulfhydryl-containing compound of the
general formula PSH are provided, in which a conjugate of general formula VI is formed from the
sulfhydryl-containing compound and the conjugate is then administered to the mammal (for example,
in an aqueous solution or an oral dosage unit).

DEPR:
The fatty acid conjugates of the present invention are soluble in most buffer solutions in which
proteins and peptides are soluble. In particular, any free carboxylic acid groups are charged at
neutral pH and therefore improve the solubility of the conjugates. This greatly facilitates the
formulation of the conjugates with suitable pharmaceutically-acceptable carriers or adjuvants for
administration of the proteins or peptides to a patient by oral or other routes.

25. Document ID: US 5907030 A

L10: Entry 25 of 42

File: USPT

May 25, 1999

US-PAT-NO: 5907030
DOCUMENT-IDENTIFIER: US 5907030 A
TITLE: Method and compositions for lipidization of hydrophilic molecules
DATE-ISSUED: May 25, 1999

US-CL-CURRENT: 530/331; 530/307, 530/317, 546/294

APPL-NO: 8/ 524362
DATE FILED: September 5, 1995

PARENT-CASE:
This application is a continuation-in-part of application Ser. No. 08/349,717 filed Jan. 25,
1995, abandoned.

IN: Shen; Wei-Chiang, Ekrami; Hossein M.

AB: Fatty acid derivatives of sulfhydryl-containing compounds (for example,
sulfhydryl-containing peptides or proteins) comprising fatty acid-conjugated products with a
disulfide linkage are employed for delivery of the compounds to mammalian cells. This
modification markedly increases the absorption of the compounds by mammalian cells relative
to the rate of absorption of the unconjugated compounds, as well as prolonging blood and
tissue retention of the compounds. Moreover, the disulfide linkage in the conjugate is quite
labile in the cells and thus facilitates intracellular release of the intact compounds from
the fatty acid moieties.

L10: Entry 25 of 42

File: USPT

May 25, 1999

DOCUMENT-IDENTIFIER: US 5907030 A
TITLE: Method and compositions for lipidization of hydrophilic molecules

BSPR:
Alternative routes of protein and peptide delivery may include the buccal, nasal, oral,
pulmonary, rectal and ocular routes. Without exception, these routes are less effective than the
parenteral routes of administration. However, these routes of protein and peptide delivery are
still far more attractive than the parenteral routes because they offer convenience and control
to the patients. The oral route is particularly attractive because it is the most convenient and
patient-compliant.

BSPR:
Mucosal barriers, which separate the inside of the body from the outside (e.g. GI, ocular,
pulmonary, rectal and nasal mucosa), comprise a layer of tightly joined cell monolayers which
strictly regulates the transport of molecules. Individual cells in barriers are joined by tight
junctions which regulate entry into the intercellular space. Hence, the mucosa is at the first
level a physical barrier, transport through which depends on either the transcellular or the
paracellular pathways [Lee, V. H. L. (1988) CRC. Critical Rev. Ther. Drug Delivery Sys. 5,
69-97].

BSPR:
In addition to providing a tight physical barrier to the transport of proteins and peptides,

mucosal barriers possess enzymes which can degrade proteins and peptides before, after, and
during their passage across the mucosa. This barrier is referred to as the enzymatic barrier. The
enzymatic barrier consists of endo- and exopeptidase enzymes which cleave proteins and peptides
at their terminals or within their structure. Enzymatic activity of several mucosa have been
studied and the results demonstrated that substantial protease activity exists in the homogenates
of buccal, nasal, rectal and vaginal mucosa of albino rabbits and that these activities are
comparable to those present in the ilium [Lee et al. (1988), supra]. Therefore, regardless of the
mucosa being considered, the enzymatic barrier present will feature strongly in the degradation
of the protein and peptide molecules.

BSPR:
In accordance with the present invention, fatty acid derivatives of sulfhydryl-containing
compounds (for example, peptides, proteins or oligonucleotides which contain or are modified to
contain sulfhydryl groups) comprising fatty acid-conjugated products with a disulfide linkage are
employed for delivery of the sulfhydryl-containing compounds to mammalian cells. This
modification markedly increases the absorption of the compounds by mammalian cells relative to
the rate of absorption of the unconjugated compounds, as well as prolonging blood and tissue
retention of the compounds. Moreover, the disulfide linkage in the conjugate is quite labile in
the cells and thus facilitates intracellular release of the intact compounds from the fatty acid
moieties. Reagents and methods for preparation of the fatty acid derivatives are also provided.

DEPR:
Pursuant to another aspect of the present invention, methods for increasing the absorption or
prolonging blood and tissue retention in a mammal of a sulfhydryl-containing compound of the
general formula PSH are provided, in which a conjugate of general formula VI is formed from the
sulfhydryl-containing compound and the conjugate is then administered to the mammal (for example,
in an aqueous solution or an oral dosage unit).

DEPR:
The fatty acid conjugates of the present invention are soluble in most buffer solutions in which
proteins and peptides are soluble. In particular, any free carboxylic acid groups are charged at
neutral pH and therefore improve the solubility of the conjugates. This greatly facilitates the
formulation of the conjugates with suitable pharmaceutically-acceptable carriers or adjuvants for
administration of the proteins or peptides to a patient by oral or other routes.

26. Document ID: US 5869040 A

L10: Entry 26 of 42 File: USPT Feb 9, 1999

US-PAT-NO: 5869040
DOCUMENT-IDENTIFIER: US 5869040 A
TITLE: Gene therapy methods and compositions
DATE-ISSUED: February 9, 1999

US-CL-CURRENT: 424/93.21; 435/320.1, 435/366, 435/69.1, 536/23.5

APPL-NO: 8/ 481814
DATE FILED: June 7, 1995

IN: Oin; Xiao-Qiang

AB: The present invention relates to uses of mutant proto-oncogenes and oncoproteins
expressed by the proto-oncogenes in inhibiting tumor growth and/or inhibiting the
transformed phenotype. The preferred oncoprotein is a dominant, interfering mutant of a
nuclear E2F transcription factor protein and is preferably a mutant E2F1 transcription
factor protein. Methods of treating a target cell are described. Treatment is accomplished
by administering to a target cell a dominant interfering mutant of a proto-oncogene in an
effective amount. Treatment is also accomplished by administering to a target cell an
oncoprotein in an effective amount. Compositions for such use are described as well.

L10: Entry 26 of 42 File: USPT Feb 9, 1999

DOCUMENT-IDENTIFIER: US 5869040 A
TITLE: Gene therapy methods and compositions

BSPR:
Mutations in the RB gene have been associated definitively with the occurrence of
retinoblastomas. RB deletion or mutation has also been observed in a variety of other human
tumors. Most notable among these other cancers are osteosarcoma as well as bone and soft-tissue
sarcomas. RB loss or mutation is also strongly implicated in small cell lung carcinoma and, to a
lesser extent, other lung cancers and esophageal carcinoma. Functional loss of RB has also been
associated with cancer of the bladder, prostate, breast and liver, as well as lymphomas and
leukemias.

DEPR:
SAOS2 human osteosarcoma RB(-/-) cells (ATCC HTB85) are grown in Dulbecco's modified Eagle's
medium (Sigma) with 10% heat-inactivated HyClone bovine serum at 37.degree. C. The transfection
procedure is a calcium phosphate method in which cells were transfected at 90% confluence.
Briefly, 20 micrograms of plasmid DNA are used in the method of De Caprio et al., Cell 54:
275-283 (1988), incorporated herein by reference. The medium is changed twice, 16 hr after
transfection.

27. Document ID: US 5844081 A

L10: Entry 27 of 42 File: USPT Dec 1, 1998

US-PAT-NO: 5844081
DOCUMENT-IDENTIFIER: US 5844081 A

TITLE: Cytostatin I
DATE-ISSUED: December 1, 1998

US-CL-CURRENT: 530/350; 435/252.3, 435/320.1, 435/325, 435/69.1, 435/71.1, 435/71.2

APPL-NO: 8/ 470298
DATE FILED: June 6, 1995

PARENT-CASE:
This is a division of application Ser. No. 08/409,731 filed Mar. 24, 1995 now U.S. Pat. No.
5,658,758.

IN: Ni; Jian, Gentz; Reiner, Yu; Guo-Liang, Rosen; Craig A.

AB: A human cytostatin I polypeptide and DNA encoding such polypeptide and a
procedure for producing such polypeptide by recombinant techniques is disclosed. Also
disclosed are methods for utilizing such polypeptide for the treatment of cancers,
particularly breast cancer, leukemias, and other metastases.

L10: Entry 27 of 42
File: USPT
Dec 1, 1998

DOCUMENT-IDENTIFIER: US 5844081 A
TITLE: Cytostatin I

BSPR:
Peptides that locally signal growth cessation and stimulate differentiation of the developing
epithelium are very important for mammary gland development. Recombinant and wild- type forms of
mammary-derived growth inhibitor (MDGI) and heart-fatty acid binding protein (FABP), which belong
to the FABP family, specifically inhibit growth of normal mouse mammary epithelial cells (MEC)
and promote morphological differentiation, stimulates its own expression and promotes milk
protein synthesis. Selective inhibition of endogenous MDGI expression in MEC by antisense
phosphorothioate oligonucleotides suppresses appearance of alveolar end buds and lowers the beta-
casein level in organ cultures. Furthermore, MDGI suppresses the mitogenic effects of EGF and EGF
antagonizes the activities of MDGI. Finally, the regulatory properties of MDGI can be fully
mimicked by an 11-amino acid sequence, represented in the COOH terminus of MDGI and a subfamily
of structurally related FABPs. MDGI is the first known growth inhibitor which promotes mammary
gland differentiation. The amount of MDGI increased dramatically with the onset of lactation
after delivery. Recent studies shows that a new posttranslational processing form of MDGI, MDGI
2, not present in lactation, was found in the bovine gland during pregnancy. (Brandt et al,
Biochem Biophy Res Comm Vol 189, p406, Nov. 30, 1992) To date, bovine, rat and mouse MDGI have
been identified but no human MDGI or MDGI-like protein.

DEPR:
The pharmaceutical compositions may be administered in a convenient manner such as by the oral
(when protected from hydrolysis or digestion), topical, intravenous, intraperitoneal,
intramuscular, subcutaneous, intranasal or intradermal routes. The pharmaceutical compositions
are administered in an amount which is effective for treating and/or prophylaxis of the specific
indication. In general, they are administered in an amount of at least about 10 .mu.g/kg body
weight and in most cases they will be administered in an amount not in excess of about 8 mg/Kg
body weight per day. In most cases, the dosage is from about 10 .mu.g/kg to about 1 mg/kg body
weight daily, taking into account the routes of administration, symptoms, etc.

28. Document ID: US 5821226 A

L10: Entry 28 of 42
File: USPT
Oct 13, 1998

US-PAT-NO: 5821226
DOCUMENT-IDENTIFIER: US 5821226 A
TITLE: BAL C-tail drug delivery molecules
DATE-ISSUED: October 13, 1998

US-CL-CURRENT: 514/12; 514/13, 514/14, 514/15, 514/16, 514/17, 514/18

APPL-NO: 8/ 482262
DATE FILED: June 7, 1995

PARENT-CASE:
This application is a continuation in part of U.S. Ser. No. 08/347,718, filed Dec. 1, 1994, now
U.S. Pat. No. 5,696,087 which is incorporated herein by reference.

IN: Tang; Jordan J. N., Wang; Chi-Sun

AB: Drug delivery conjugates of including a BAL C-tail peptide including all or a
portion of the carboxy terminal region of human bile salt-activated lipase (BAL) conjugated
to a biologically active substance are described. The C-tail peptide-drug conjugates, when
orally ingested, compete with native BAL in binding to the intestinal surface, and, as a
result, permit drug compositions to be delivered specifically to the intestine. Useful
C-tail peptides are derivatives of the carboxy terminal region of BAL derived from all or
portion of the region containing amino acid residues 539 to 722, and have a mucin-like
structure containing at least three of the repeating proline-rich units of eleven amino acid
residues each.

L10: Entry 28 of 42
File: USPT
Oct 13, 1998

DOCUMENT-IDENTIFIER: US 5821226 A
TITLE: BAL C-tail drug delivery molecules

BSPR:
Drug delivery takes a variety of forms, depending on the agent to be delivered and the
administration route. A preferred mode of administration is non-invasive; i.e., administration
via oral passages. Some compounds are not suited for such administration, however, since they are
degraded by conditions in the gastrointestinal tract or do not penetrate well into the blood
stream.

BSPR:
The BAL C-tail is attached a substance to be delivered, using standard technology, either directly to the compound or to a pharmaceutical carrier for the compound. Examples of useful carriers include microspheres. Examples of useful therapeutics in addition to dietary aids include vaccines for oral administration. The C-tail fragments offers a significant advance in the art of the pharmaceutical delivery devices, in that they specifically deliver the bioactive composition to the intestine where it exerts a therapeutic effect. The C-tails can also be used to screen for compounds that affect binding of BAL to the receptor.

DEPR:
Compositions including all or a portion of the carboxy terminal (C tail) region of bile salt-activated lipase (BAL), or functional equivalents thereof, (C-tail peptides) are described, which, in the intestine, compete with native BAL in binding to the intestinal surface, and which are conjugated to a biologically active composition. The BAL C-tail molecules are attached to a substance to be delivered thus enabling the substance to be delivered specifically to the intestine upon oral administration of the conjugate. In the intestine, these compositions bind to the intestinal surface resulting in delivery and/or long-term presence of the therapeutic compound at the intestinal lining.

DEPR:
Examples of useful proteins include hormones such as insulin, growth hormones including somatometins, transforming growth factors, and other growth factors, antigens for oral vaccines, enzymes such as lactase or lipases, and digestive aids such as pancreatin.

DEPR:
Pharmaceutical compositions containing the C-tail-bioactive agent conjugate, designed to improve the pharmaceutical activity of the C-tail protein-drug conjugate when administered to a patient in a therapeutically effective amount, can be prepared in combination with appropriate pharmaceutical stabilization compounds, delivery vehicles, carriers, inert diluents, and/or other additives appropriate for enteral (oral) administration according to methods well known in the art. The formulation usually provides for release within the stomach or the intestine. The C-tail protein-drug conjugate can be formulated into a liquid, paste, suspension, gel, powder, tablet, capsule, food additive or other standard form. Pharmaceutically compatible binding agents and/or adjuvant materials can be included as part of the composition. Examples include a binder such as microcrystalline cellulose, gum tragacanth, or gelatin; an excipient such as starch or lactose; a disintegrating agent such as alginic acid, Primogen.TM., or corn starch; a lubricant such as magnesium stearate or sterotes; aglidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; and/or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier. Other dosage unit forms may further include coatings of sugar, shellac, or other enteric agents. The C-tail protein-drug can be administered as a component of a fluid such as an elixir, suspension, beverage, liquid dietary supplement or substitute, or syrup; or of a solid such as a wafer or candy. The C-tail protein-drug can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action.

DEPR:
In one preferred embodiment, C-tail-drug is encapsulated within carriers that effect release in the small intestine, such as microparticles, microcapsules, or microspheres prepared from synthetic or natural polymers such as proteins, polyhydroxy acids, or polysaccharides.
Appropriate systems are known to those skilled in the art. Several microsphere formulations have been proposed as a means for oral drug delivery. These formulations generally serve to protect the encapsulated compound and to deliver the compound into the blood stream. Enteric coated formulations have been widely used for many years to protect drugs administered orally, as well as to delay release. Other formulations designed to deliver compounds into the blood stream, as well as to protect the encapsulated drug, are formed of a hydrophobic protein, such as zein, as described in PCT/US90/06430 and PCT/US90/06433; "proteinoids", as described in U.S. Pat. No. 4,976,968 to Steiner; or synthetic polymers, as described in European Patent application 0 333 523 by the UAB Research Foundation and Southern Research Institute. EPA 0 333 523 described microparticles of less than ten microns in diameter that contain antigens, for use in oral administration of vaccines. Larger sizes are preferred for the uses described herein to avoid uptake into the blood and lymph systems of the encapsulated C-tail protein.

DEPL:
Oral Administration

DETL:

SEQUENCE LISTING (1)
GENERAL INFORMATION: (iii) NUMBER OF SEQUENCES: 3 (2) INFORMATION FOR SEQ ID NO:1: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 722 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: protein (iii) HYPOTHETICAL: NO (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

AlaLysLeuGlyAlaValTyrThrGluGlyGlyPheValGluGlyVal 151015
AsnLysLysLeuGlyLeuLeuGlyAspSerValAspIlePheLysGly 202530
IleProPheAlaAlaProThrLysAlaLeuGluAsnProGlnProHis 354045
ProGlyTrpGlnGlyThrLeuLysAlaLysAsnPheLysLysArgCys 505560
LeuGlnAlaThrIleThrGlnAspSerThrTyrGlyAspGluAspCys 65707580
LeuTyrLeuAsnIleTrpValProGlnGlyArgLysGlnValSerArg 859095
AspLeuProValMetIleTrpIleTyrGlyGlyAlaPheLeuMetGly 100105110
SerGlyHisGlyAlaAsnPheLeuAsnAsnTyrLeuTyrAspGlyGlu 115120125
GluIleAlaThrArgGlyAsnValIleValValThrPheAsnTyrArg 130135140
ValGlyProLeuGlyPheLeuSerThrGlyAspAlaAsnLeuProGly 145150155160
AsnTyrGlyLeuArgAspGlnHisMetAlaIleAlaTrpValLysArg 165170175
AsnIleAlaAlaPheGlyGlyAspProAsnAsnIleThrLeuPheGly 180185190
GluSerAlaGlyGlyAlaSerValSerLeuGlnThrLeuSerProTyr 195200205
AsnLysGlyLeuIleArgArgAlaIleSerGlnSerGlyValAlaLeu 210215220
SerProTrpValIleGlnLysAsnProLeuPheTrpAlaLysLysVal 225230235240
AlaGluLysValGlyCysProValGlyAspAlaAlaArgMetAlaGln 245250255
CysLeuLysValThrAspProArgAlaLeuThrLeuAlaTyrLysVal 260265270
ProLeuAlaGlyLeuGluTyrProMetLeuHisTyrValGlyPheVal 275280285
ProValIleAspGlyAspPheIleProAlaAspProIleAsnLeuTyr 290295300
AlaAsnAlaAlaAspIleAspTyrIleAlaGlyThrAsnAsnMetAsp 305310315320
GlyHisIlePheAlaSerIleAspMetProAlaIleAsnLysGlyAsn 325330335
LysLysValThrGluGluAspPheTyrLysLeuValSerGluPheThr 340345350
IleThrLysGlyLeuArgGlyAlaLysThrThrPheAspValTyrThr 355360365
GluSerTrpAlaGlnAspProSerGlnGluAsnLysLysLysThrVal 370375380
ValAspPheGluThrAspValLeuPheLeuValProThrGluIleAla 385390395400
LeuAlaGlnHisArgAlaAsnAlaLysSerAlaLysThrTyrAlaTyr 405410415
LeuPheSerHisProSerArgMetProValTyrProLysTrpValGly 420425430
AlaAspHisAlaAspAspIleGlnTyrValPheGlyLysProPheAla 435440445
ThrProThrGlyTyrArgProGlnAspArgThrValSerLysAlaMet 450455460
IleAlaTyrTrpThrAsnPheAlaLysThrGlyAspProAsnMetGly 465470475480
AspSerAlaValProThrHisTrpGluProTyrThrThrGluAsnSer 485490495

GlyTyrLeuGluIleThrLysLysMetGlySerSerSerMetLysArg 500505510
SerLeuArgThrAsnPheLeuArgTyrTrpThrLeuThrTyrLeuAla 515520525
LeuProThrValThrAspGlnGluAlaThrProValProProThrGly 530535540
AspSerGluAlaThrProValProProThrGlyAspSerGluThrAla 545550555560
ProValProProThrGlyAspSerGlyAlaProProValProProThr 565570575
GlyAspSerGlyAlaProProValProProThrGlyAspSerGlyAla 580585590
ProProValProProThrGlyAspSerGlyAlaProProValProPro 595600605
ThrGlyAspSerGlyAlaProProValProProThrGlyAspSerGly 610615620
AlaProProValProProThrGlyAspSerGlyAlaProProValPro 625630635640
ProThrGlyAspAlaGlyProProProProValProProThrGlyAspSer 645650655
GlyAlaProProValProProThrGlyAspSerGlyAlaProProVal 660665670
ThrProThrGlyAspSerGluThrAlaProValProProThrGlyAsp 675680685
SerGlyAlaProProValProProThrGlyAspSerGluAlaAlaPro 690695700
ValProProThrAspAspSerLysGluAlaGlnMetProAlaValIle 705710715720

ArgPhe (2) INFORMATION FOR SEQ ID
NO:2: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 742 amino acids (B) TYPE: amino acid (D)
TOPOLOGY: linear (ii) MOLECULE TYPE: protein (iii) HYPOTHETICAL: NO (v) FRAGMENT TYPE: internal
(ix) FEATURE: (A) NAME/KEY: Modified-site (B) LOCATION: 186..187 (D) OTHER INFORMATION: /note=
"Position 187 represents a potential N- linked glycosylation site." (ix) FEATURE: (A) NAME/KEY:
Modified-site (B) LOCATION: 193..194 (D) OTHER INFORMATION: /note= "The serine at position 194
represents an active site serine." (ix) FEATURE: (A) NAME/KEY: misc. feature (B) LOCATION: 1..742
(D) OTHER INFORMATION: /Function = "Amino acid sequence for the Human Milk Bile-Salt-activated
Lipase." (xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

MetGlyArgLeuGlnLeuValValLeuGlyLeuThrCysCysTrpAla
151015 ValAlaSerAlaAlaLysLeuGlyAlaValTyrThrGluGlyGlyPhe 202530
ValGluGlyValAsnLysLysLeuGlyLeuLeuGlyAspSerValAsp 354045
IlePheLysGlyIleProPheAlaAlaProThrLysAlaLeuGluAsn 505560
ProGlnProHisProGlyTrpGlnGlyThrLeuLysAlaLysAsnPhe 65707580
LysLysArgCysLeuGlnAlaThrIleThrGlnAspSerThrTyrGly 859095
AspGluAspCysLeuTyrLeuAsnIleTrpValProGlnGlyArgLys 100105110
GlnValSerArgAspLeuProValMetIleTrpIleTyrGlyGlyAla 115120125
PheLeuMetGlySerGlyHisGlyAlaAsnPheLeuAsnAsnTyrLeu 130135140
TyrAspGlyGluGluIleAlaThrArgGlyAsnValIleValValThr 145150155160
PheAsnTyrArgValGlyProLeuGlyPheLeuSerThrGlyAspAla 165170175
AsnLeuProGlyAsnTyrGlyLeuArgAspGlnHisMetAlaIleAla 180185190
TrpValLysArgAsnIleAlaAlaPheGlyGlyAspProAsnAsnIle 195200205
ThrLeuPheGlyGluSerAlaGlyGlyAlaSerValSerLeuGlnThr 210215220
LeuSerProTyrAsnLysGlyLeuIleArgArgAlaIleSerGlnSer 225230235240
GlyValAlaLeuSerProTrpValIleGlnLysAsnProLeuPheTrp 245250255
AlaLysLysValAlaGluLysValGlyCysProValGlyAspAlaAla 260265270
ArgMetAlaGlnCysLeuLysValThrAspProArgAlaLeuThrLeu 275280285
AlaTyrLysValProLeuAlaGlyLeuGluTyrProMetLeuHisTyr 290295300
ValGlyPheValProValIleAspGlyAspPheIleProAlaAspPro 305310315320
IleAsnLeuTyrAlaAsnAlaAlaAspIleAspTyrIleAlaGlyThr 325330335
AsnAsnMetAspGlyHisIlePheAlaSerIleAspMetProAlaIle 340345350
AsnLysGlyAsnLysLysValThrGluGluAspPheTyrLysLeuVal 355360365
SerGluPheThrIleThrLysGlyLeuArgGlyAlaLysThrThrPhe 370375380
AspValTyrThrGluSerTrpAlaGlnAspProSerGlnGluAsnLys 385390395400
LysLysThrValValAspPheGluThrAspValLeuPheLeuValPro 405410415
ThrGluIleAlaLeuAlaGlnHisArgAlaAsnAlaLysSerAlaLys 420425430
ThrTyrAlaTyrLeuPheSerHisProSerArgMetProValTyrPro 435440445
LysTrpValGlyAlaAspHisAlaAspAspIleGlnTyrValPheGly 450455460
LysProPheAlaThrProThrGlyTyrArgProGlnAspArgThrVal 465470475480
SerLysAlaMetIleAlaTyrTrpThrAsnPheAlaLysThrGlyAsp 485490495
ProAsnMetGlyAspSerAlaValProThrHisTrpGluProTyrThr 500505510
ThrGluAsnSerGlyTyrLeuGluIleThrLysLysMetGlySerSer 515520525
SerMetLysArgSerLeuArgThrAsnPheLeuArgTyrTrpThrLeu 530535540
ThrTyrLeuAlaLeuProThrValThrAspGlnGluAlaThrProVal 545550555560
ProProThrGlyAspSerGluAlaThrProValProProThrGlyAsp 565570575
SerGluThrAlaProValProProThrGlyAspSerGlyAlaProPro 580585590
ValProProThrGlyAspSerGlyAlaProProValProProThrGly 595600605
AspSerGlyAlaProProValProProThrGlyAspSerGlyAlaPro 610615620
ProValProProThrGlyAspSerGlyAlaProProValProProThr 625630635640
GlyAspSerGlyAlaProProValProProThrGlyAspSerGlyAla 645650655
ProProValProProThrGlyAspAlaGlyProProProProValProPro 660665670
ThrGlyAspSerGlyAlaProProValProProThrGlyAspSerGly 675680685
AlaProProValThrProThrGlyAspSerGluThrAlaProValPro 690695700
ProThrGlyAspSerGlyAlaProProValProProThrGlyAspSer 705710715720
GluAlaAlaProValProProThrAspAspSerLysGluAlaGlnMet 725730735

ProAlaValIleArgPhe 740 (2) INFORMATION
FOR SEQ ID NO:3: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 3018 base pairs (B) TYPE: nucleic acid
(C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: cDNA (iii) HYPOTHETICAL: NO
(iv) ANTI-SENSE: NO (ix) FEATURE: (A) NAME/KEY: misc. feature (B) LOCATION: 1..742 (D) OTHER
INFORMATION: /Function = "Nucleotides 679 through 2904 encode the amino acid sequence for the
Human Milk Bile Salt- activated Lipase." (xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

CTCAATTGGAGGATCAAAGTTGAGAAAAGTAATATTCGACATTTTT
CGATTCAACGGAGT60

GGCCACCAAGACGATGTCATAGAAGTCTGAACGAGTCTCAGTTCC
AATTTGGTAGACCAC120

TTCATACATCTTTGTTGGATTTCCTGTGTACTTGGTCTTTGTTTTCT
CCTCGATGTACAT180

TACTGAGCCAGATATAAGATTGCTTTTGGATGCCTGCAGAAGCCCT
GAGCAAACAAGTTT240

ATTGCCACCTTCTACTGCCCAAAGGCCAGAATCAGAACAGGACAG
TGACACCGCCCCCAC300

AAAGGCATTGATGTCCGTGCTTTGGCCATAATTGACCCTCATAACA
GGAGCAATCATTTC360

ATTGAGGAACTTCTCAGAAAAGCCGGCCTTTTGCAAGGTTTCAAG
AAGTGTTCGATTAAG420

CATTCCAAGGAAGTCATCTCCTCCTAGAGCATGAAGTAATTTTTCG
ACACTACTGAAGGC480

ATAGTCATGAGACTGGTAGCGGTAGATCCTCATGAACTTGTCTAA
CACGTCCTCTACCCA540

CATGTGCATACGGAGGGATTGAAATCCATAGCGCCAAACTAATTT
AATCACGTTAATTAT600

GAACCAGTTGCTCTCCTCAAATACCAGAGTCTCTCCATTATATATC
CCCAGTAGGCCACC660

CAGAGGCTGATGCTCACCATGGGGCGCCTGCAACTGGTTGTGTTG
GGCCTCACCTGCTGC720

TGGGCAGTGGCGAGTGCCGCGAAGCTGGGCGCCGTGTACACAGA
AGGTGGGTTCGTGGAA780

GGCGTCAATAAGAAGCTCGGCCTCCTGGGTGACTCTGTGGACATC
TTCAAGGGCATCCCC840

TTCGCAGCTCCCACCAAGGCCCTGGAAAATCCTCAGCCACATCCT
GGCTGGCAAGGGACC900

CTGAAGGCCAAGAACTTCAAGAAGAGATGCCTGCAGGCCACCATC
ACCCAGGACAGCACC960

TACGGGGATGAAGACTGCCTGTACCTCAACATTTGGGTGCCCCAG
GGCAGGAAGCAAGTC1020

TCCCGGGACCTGCCCGTTATGATCTGGATCTATGGAGGCGCCTTCC
TCATGGGGTCCGGC1080

CLPR:
28. The composition of claim 14 wherein the C-tail protein is in a dietary formulation for oral
administration.

CLPV:
orally administering to an individual in need thereof a therapeutically effective amount of a
C-tail protein conjugated to a therapeutic composition, in combination with a pharmaceutical
carrier acceptable for oral administration,

CLPV:
a therapeutically effective amount of a C-tail protein conjugated to a

therapeutic composition,
in combination with a pharmaceutical carrier acceptable for oral administration,

29. Document ID: US 5792751 A

L10: Entry 29 of 42

File: USPT

Aug 11, 1998

US-PAT-NO: 5792751
DOCUMENT-IDENTIFIER: US 5792751 A
TITLE: Tranformation of cells associated with fluid spaces
DATE-ISSUED: August 11, 1998

US-CL-CURRENT: 514/44; 435/320.1

APPL-NO: 8/ 184547
DATE FILED: January 21, 1994

PARENT-CASE:
This application is a continuation-in-part of U.S. patent application Ser. No. 08/181,707, filed Jan. 13, 1994, (entitled "Somatic Gene Therapy", by Ledley, F. D. et al. and bearing attorney docket number 205/127) now abandoned, which is a continuation-in-part of U.S. patent application Ser. No. 07/912,934, filed Jul. 13, 1992, (entitled "Targeting Somatic Gene Therapy" by Ledley, F. D.) now abandoned, and is also a continuation-in-part of U.S. patent application Ser. No. 07/868,061, filed Apr. 131 1992, (entitled "Targeting Somatic Gene Therapy to the Thyroid" by Ledley, F. D.) now abandoned, the whole of which (including drawings) are hereby incorporated by reference. This application is also a continuation-in-part of PCT Application No. PCT/US93/06479, filed Jul. 9, 1993, entitled "Targeting Somatic Gene Therapy To The Joints" by Ledley, F. D. et al. and assigned attorney docket no. 204/019-PCT.

IN: Ledley; Fred D., O'Malley, Jr.; Bert W.

AB: This invention relates to the transfer and expression of genes in cells associated with fluid spaces, such as follicles of the thyroid, the synovium of the joint, the vitreous of the eye and the inner or middle ear. Formulated DNA expression vectors comprising a gene are introduced with or without formulation elements directly into a fluid space under conditions in which the cells associated with the fluid space can incorporate the formulated DNA expression vector and express the transformed gene.

L10: Entry 29 of 42

File: USPT

Aug 11, 1998

DOCUMENT-IDENTIFIER: US 5792751 A
TITLE: Tranformation of cells associated with fluid spaces

BSPR:
Another important embodiment of the present invention is a novel application of genetically modified receptors for regulating expression of recombinant gene products as disclosed in U.S. patent application, Ser. No. 07/882,771, entitled "Mutated Steroid Hormone Receptors and Methods for Their Use", O'Malley et al., filed May 14, 1992, and hereby incorporated by reference (including drawings). O'Malley et al., describe modified receptors expressed by formulated DNA expression vectors to control the level of expression of recombinant gene products. The steroid receptor family of gene regulatory proteins is an ideal set of such molecules. These proteins are ligand activated transcription factors whose ligands can range from steroids to retinoids, fatty acids, vitamins, thyroid hormones and other presently unidentified small molecules. These compounds bind to receptors and either up-regulate or down-regulate transcription.

BSPR:
The vectors of the above methods may be administered by various routes. The term "administration" refers to the route of introduction of a formulated vector into the body. Administration may be intravenous, intramuscular, topical, oral, or by gene gun or hypospray instrumentation. Administration can be directly to a target tissue or through systemic delivery. In the preferred embodiment, systemic delivery involves intravenous administration. Administration directly to the target tissue can involve needle injection, hypospray, electroporation, or the gene gun. See, e.g., WO 93/18759, hereby incorporated by reference herein. The preferred embodiment is by direct injection.

DEPR:
Administration as used herein refers to the route of introduction of a vector or carrier of DNA into the body. Administration may include intravenous, intramuscular, topical, or oral methods of delivery. Administration can be directly to a target tissue or through systemic delivery.

30. Document ID: US 5770580 A

L10: Entry 30 of 42

File: USPT

Jun 23, 1998

US-PAT-NO: 5770580
DOCUMENT-IDENTIFIER: US 5770580 A
TITLE: Somatic gene therapy to cells associated with fluid spaces
DATE-ISSUED: June 23, 1998

US-CL-CURRENT: 514/44; 435/320.1, 435/325, 435/69.1

APPL-NO: 8/ 453501
DATE FILED: May 30, 1995

PARENT-CASE:
This application is a divisional of application Ser. No. 08/184,547, by Ledley et al., filed Jan. 21, 1994, entitled "Somatic Gene Therapy to Cells Associated with Fluid Spaces." The 08/184,547 application is a continuation-in-part of Ledley et al., application Ser. No. 08/181,707, now abandoned, filed Jan. 13, 1994, entitled "Somatic Gene Therapy." Both the above referenced continuation-in-part applications are hereby incorporated by reference (including drawings). In addition, the 08/181,707 application is also a continuation-in-part of Ledley, application Ser.

No. 07/912,934, now abandoned filed Jul. 13, 1992, entitled "Targeting Somatic Gene Therapy to
the Joints," and also a continuation-in-part of Ledley et al., application Ser. No. 07/868,061,
now abandoned, filed Apr. 13, 1992, entitled "Targeting Somatic Gene Therapy to the Thyroid," the
whole of which (including drawings) are both hereby incorporated by reference.

IN: Ledley; Fred D., O'Malley, Jr.; Bert W.

AB: This invention relates to somatic gene therapy to cells associated with fluid
spaces, such as follicles of the thyroid, the synovium of the joint, the vitreous of the eye
and the inner or middle ear. Formulated DNA expression vectors are introduced with or
without formulation elements into fluid spaces under conditions in which cells associated
with the fluid space can incorporate the formulated DNA expression vector. Formulated DNA
expression-mediated gene therapy allows treatment of diseases involving cells associated
with fluid spaces.

L10: Entry 30 of 42

File: USPT

Jun 23, 1998

DOCUMENT-IDENTIFIER: US 5770580 A
TITLE: Somatic gene therapy to cells associated with fluid spaces

BSPR:
Another important embodiment of the present invention is a novel application of genetically
modified receptors for regulating expression of recombinant gene products as disclosed in U.S.
Pat. application, Ser. No. 07/882,771, entitled "Mutated Steroid Hormone Receptors and Methods
for Their Use", O'Malley et al., filed May 14, 1992, and hereby incorporated by reference
(including drawings). O'Malley et al., describe modified receptors expressed by formulated DNA
expression vectors to control the level of expression of recombinant gene products. The steroid
receptor family of gene regulatory proteins is an ideal set of such molecules. These proteins are
ligand activated transcription factors whose ligands can range from steroids to retinoids, fatty
acids, vitamins, thyroid hormones and other presently unidentified small molecules. These
compounds bind to receptors and either up-regulate or down-regulate transcription.

BSPR:
The vectors of the above methods may be administered by various routes. The term "administration"
refers to the route of introduction of a formulated vector into the body. Administration may be
intravenous, intramuscular, topical, oral, or by gene gun or hypospray instrumentation.
Administration can be directly to a target tissue or through systemic delivery. In the preferred
embodiment, systemic delivery involves intravenous administration. Administration directly to the
target tissue can involve needle injection, hypospray, electroporation, or the gene gun. See,
e.g., WO 93/18759, hereby incorporated by reference herein. The preferred embodiment is by direct
injection.

DEPR:
Administration as used herein refers to the route of introduction of a vector or carrier of DNA
into the body. Administration may include intravenous, intramuscular, topical, or oral methods of
delivery. Administration can be directly to a target tissue or through systemic delivery.

31. Document ID: US 5696087 A

L10: Entry 31 of 42

File: USPT

Dec 9, 1997

US-PAT-NO: 5696087
DOCUMENT-IDENTIFIER: US 5696087 A
TITLE: Method and compositions for reducing cholesterol absorption
DATE-ISSUED: December 9, 1997

US-CL-CURRENT: 514/12; 514/13, 514/14, 514/15, 514/16, 514/17, 514/18

APPL-NO: 8/ 347718
DATE FILED: December 1, 1994

IN: Tang; Jordan J. N., Wang; Chi-Sun

AB: Compositions including all or a portion and chemically or recombinantly
synthesized analogues of the carboxy terminal region of bile salt-activated lipase (BAL) are
described, which, when orally ingested, compete with native BAL in binding to the intestinal
surface and thus reduce the amount of cholesterol taken into the blood stream.

L10: Entry 31 of 42

File: USPT

Dec 9, 1997

DOCUMENT-IDENTIFIER: US 5696087 A
TITLE: Method and compositions for reducing cholesterol absorption

DEPR:
Pharmaceutical compositions containing BAL C-tail, designed to improve the pharmaceutical
activity of C-tail when administered to a patient in an amount effective to reduce cholesterol
uptake in the intestine and thereby decrease blood cholesterol levels, can be prepared in
combination with appropriate pharmaceutical stabilization compounds, delivery vehicles, carriers,
inert diluents, and/or other additives appropriate for enteral (oral) administration according to
methods well known in the art. The formulation usually provides for release within the stomach or
the intestine. The BAL C-tail can be formulated into a liquid, paste, suspension, gel, powders,
tablets, capsules, food additives or other standard forms. Pharmaceutically compatible binding
agents and/or adjuvant materials can be included as part of the composition. Examples include a
binder such as microcrystalline cellulose, gum tragacanth, or gelatins an excipient such as
starch or lactose; a disintegrating agent such as alginic acid, Primogen.TM., or corn starch; a
lubricant such as magnesium stearate or sterotes; aglidant such as colloidal silicon dioxide; a
sweetening agent such as sucrose or saccharin; and/or a flavoring agent such as peppermint,

methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it can contain,
in addition to material of the above type, a liquid carrier. Other dosage unit forms may further
include coatings of sugar, shellac, or other enteric agents. The BAL C-tail can be administered
as a component of a fluid such as an elixir, suspension, beverage, liquid dietary supplement or
substitute, or syrup; or of a solid such as a wafer or candy. The BAL C-tail can also be mixed
with other active materials that do not impair the desired action, or with materials that
supplement the desired action, such as other blood lipid-lowering pharmaceutical compositions.

DEPR:
In one preferred embodiment, BAL C-tail is encapsulated within carriers that effect release in
the small intestine, such as microparticles, microcapsules, or microspheres prepared from
synthetic or natural polymers such as proteins, polyhydroxy acids, or polysaccharides.
Appropriate systems are known to those skilled in the art. Several microsphere formulations have
been proposed as a means for oral drug delivery. These formulations generally serve to protect
the encapsulated compound and to deliver the compound into the blood stream. Enteric coated
formulations have been widely used for many years to protect drugs administered orally, as well
as to delay release. Other formulations designed to deliver compounds into the blood stream, as
well as to protect the encapsulated drug, are formed of a hydrophobic protein, such as zein, as
described in PCT/US90/06430 and PCT/US90/06433; "proteinoids", as described in U.S. Pat. No.
4,976,968 to Steiner; or synthetic polymers, as described in European Patent application 0 333
t23 by the UAB Research Foundation and Southern Research Institute. EPA 0 333 523 described
microparticles of less than ten microns in diameter that contain antigens, for use in oral
administration of vaccines. Larger sizes are preferred for the uses described herein to avoid
uptake into the blood and lymph systems of the encapsulated BAL C-tail.

DETL:

SEQUENCE LISTING (1)
GENERAL INFORMATION: (iii) NUMBER OF SEQUENCES: 6 (2) INFORMATION FOR SEQ ID NO:1: (i) SEQUENCE
CHARACTERISTICS: (A) LENGTH: 722 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii)
MOLECULE TYPE: protein (iii) HYPOTHETICAL: NO (v) FRAGMENT TYPE: internal (xi) SEQUENCE
DESCRIPTION: SEQ ID NO:1:
AlaLysLeuGlyAlaValTyrThrGluGlyGlyPheValGluGlyVal 151015
AsnLysLysLeuGlyLeuLeuGlyAspSerValAspIlePheLysGly 202530
IleProPheAlaAlaProThrLysAlaLeuGluAsnProGlnProHis 354045
ProGlyTrpGlnGlyThrLeuLysAlaLysAsnPheLysLysArgCys 505560
LeuGlnAlaThrIleThrGlnAspSerThrTyrGlyAspGluAspCys 65707580
LeuTyrLeuAsnIleTrpValProGlnGlyArgLysGlnValSerArg 859095
AspLeuProValMetIleTrpIleTyrGlyGlyAlaPheLeuMetGly 100105110
SerGlyHisGlyAlaAsnPheLeuAsnAsnTyrLeuTyrAspGlyGlu 115120125
GluIleAlaThrArgGlyAsnValIleValValThrPheAsnTyrArg 130135140
ValGlyProLeuGlyPheLeuSerThrGlyAspAlaAsnLeuProGly 145150155160
AsnTyrGlyLeuArgAspGlnHisMetAlaIleAlaTrpValLysArg 165170175
AsnIleAlaAlaPheGlyGlyAspProAsnAsnIleThrLeuPheGly 180185190
GluSerAlaGlyGlyAlaSerValSerLeuGlnThrLeuSerProTyr 195200205
AsnLysGlyLeuIleArgArgAlaIleSerGlnSerGlyValAlaLeu 210215220
SerProTrpValIleGlnLysAsnProLeuPheTrpAlaLysLysVal 225230235240
AlaGluLysValGlyCysProValGlyAspAlaAlaArgMetAlaGln 245250255
CysLeuLysValThrAspProArgAlaLeuThrLeuAlaTyrLysVal 260265270
ProLeuAlaGlyLeuGluTyrProMetLeuHisTyrValGlyPheVal 275280285
ProValIleAspGlyAspPheIleProAlaAspProIleAsnLeuTyr 290295300
AlaAsnAlaAlaAspIleAspTyrIleAlaGlyThrAsnAsnMetAsp 305310315320
GlyHisIlePheAlaSerIleAspMetProAlaIleAsnLysGlyAsn 325330335
LysLysValThrGluGluAspPheTyrLysLeuValSerGluPheThr 340345350
IleThrLysGlyLeuArgGlyAlaLysThrThrPheAspValTyrThr 355360365
GluSerTrpAlaGlnAspProSerGlnGluAsnLysLysLysThrVal 370375380
ValAspPheGluThrAspValLeuPheLeuValProThrGluIleAla 385390395400
LeuAlaGlnHisArgAlaAsnAlaLysSerAlaLysThrTyrAlaTyr 405410415
LeuPheSerHisProSerArgMetProValTyrProLysTrpValGly 420425430
AlaAspHisAlaAspAspIleGlnTyrValPheGlyLysProPheAla 435440445
ThrProThrGlyTyrArgProGlnAspArgThrValSerLysAlaMet 450455460
IleAlaTyrTrpThrAsnPheAlaLysThrGlyAspProAsnMetGly 465470475480
AspSerAlaValProThrHisTrpGluProTyrThrThrGluAsnSer 485490495
GlyTyrLeuGluIleThrLysLysMetGlySerSerSerMetLysArg 500505510
SerLeuArgThrAsnPheLeuArgTyrTrpThrLeuThrTyrLeuAla 515520525
LeuProThrValThrAspGlnGluAlaThrProValProProThrGly 530535540
AspSerGluAlaThrProValProProThrGlyAspSerGluThrAla 545550555560
ProValProProThrGlyAspSerGlyAlaProProValProProThr 565570575
GlyAspSerGlyAlaProProValProProThrGlyAspSerGlyAla 580585590
ProProValProProThrGlyAspSerGlyAlaProProValProPro 595600605
ThrGlyAspSerGlyAlaProProValProProThrGlyAspSerGly 610615620
AlaProProValProProThrGlyAspSerGlyAlaProProValPro 625630635640
ProThrGlyAspAlaGlyProProProValProProThrGlyAspSer 645650655
GlyAlaProProValProProThrGlyAspSerGlyAlaProProVal 660665670
ThrProThrGlyAspSerGluThrAlaProValProProThrGlyAsp 675680685
SerGlyAlaProProValProProThrGlyAspSerGluAlaAlaPro 690695700
ValProProThrAspAspSerLysGluAlaGlnMetProAlaValIle 705710715720
ArgPhe (2) INFORMATION FOR SEQ ID
NO:2: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 742 amino acids (B) TYPE: amino acid (D)
TOPOLOGY: linear (ii) MOLECULE TYPE: protein (iii) HYPOTHETICAL: NO (v) FRAGMENT TYPE: internal
(ix) FEATURE: (A) NAME/KEY: Modified-site (B) LOCATION: 186..187 (D) OTHER INFORMATION:
/note="Position 187 represents a potential N- linked glycosylation site." (ix) FEATURE: (A)
NAME/KEY: Modified-site (B) LOCATION: 193..194 (D) OTHER INFORMATION: /note="The serine at
position 194 represents an active site serine." (ix) FEATURE: (A) NAME/KEY: misc. feature (B)
LOCATION: 1..742 (D) OTHER INFORMATION: /Function ="Amino acid sequence for the Human Milk Bile
Salt-activated Lipase." (xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:
MetGlyArgLeuGlnLeuValValLeuGlyLeuThrCysCysTrpAla 151015
ValAlaSerAlaAlaLysLeuGlyAlaValTyrThrGluGlyGlyPhe 202530
ValGluGlyValAsnLysLysLeuGlyLeuLeuGlyAspSerValAsp 354045
IlePheLysGlyIleProPheAlaAlaProThrLysAlaLeuGluAsn 505560
ProGlnProHisProGlyTrpGlnGlyThrLeuLysAlaLysAsnPhe 65707580
LysLysArgCysLeuGlnAlaThrIleThrGlnAspSerThrTyrGly 859095
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GlnValSerArgAspLeuProValMetIleTrpIleTyrGlyGlyAla 115120125
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TyrAspGlyGluGluIleAlaThrArgGlyAsnValIleValValThr 145150155160
PheAsnTyrArgValGlyProLeuGlyPheLeuSerThrGlyAspAla 165170175
AsnLeuProGlyAsnTyrGlyLeuArgAspGlnHisMetAlaIleAla 180185190
TrpValLysArgAsnIleAlaAlaPheGlyGlyAspProAsnAsnIle 195200205
ThrLeuPheGlyGluSerAlaGlyGlyAlaSerValSerLeuGlnThr 210215220
LeuSerProTyrAsnLysGlyLeuIleArgArgAlaIleSerGlnSer 225230235240
GlyValAlaLeuSerProTrpValIleGlnLysAsnProLeuPheTrp 245250255
AlaLysLysValAlaGluLysValGlyCysProValGlyAspAlaAla 260265270
ArgMetAlaGlnCysLeuLysValThrAspProArgAlaLeuThrLeu 275280285
AlaTyrLysValProLeuAlaGlyLeuGluTyrProMetLeuHisTyr 290295300
ValGlyPheValProValIleAspGlyAspPheIleProAlaAspPro 305310315320
IleAsnLeuTyrAlaAsnAlaAlaAspIleAspTyrIleAlaGlyThr 325330335
AsnAsnMetAspGlyHisIlePheAlaSerIleAspMetProAlaIle 340345350
AsnLysGlyAsnLysLysValThrGluGluAspPheTyrLysLeuVal 355360365
SerGluPheThrIleThrLysGlyLeuArgGlyAlaLysThrThrPhe 370375380
AspValTyrThrGluSerTrpAlaGlnAspProSerGlnGluAsnLys 385390395400
LysLysThrValValAspPheGluThrAspValLeuPheLeuValPro 405410415
ThrGluIleAlaLeuAlaGlnHisArgAlaAsnAlaLysSerAlaLys 420425430
ThrTyrAlaTyrLeuPheSerHisProSerArgMetProValTyrPro 435440445
LysTrpValGlyAlaAspHisAlaAspAspIleGlnTyrValPheGly 450455460
LysProPheAlaThrProThrGlyTyrArgProGlnAspArgThrVal 465470475480
SerLysAlaMetIleAlaTyrTrpThrAsnPheAlaLysThrGlyAsp 485490495
ProAsnMetGlyAspSerAlaValProThrHisTrpGluProTyrThr 500505510
ThrGluAsnSerGlyTyrLeuGluIleThrLysLysMetGlySerSer 515520525
SerMetLysArgSerLeuArgThrAsnPheLeuArgTyrTrpThrLeu 530535540
ThrTyrLeuAlaLeuProThrValThrAspGlnGluAlaThrProVal 545550555560
ProProThrGlyAspSerGluAlaThrProValProProThrGlyAsp 565570575
SerGluThrAlaProValProProThrGlyAspSerGlyAlaProPro 580585590
ValProProThrGlyAspSerGlyAlaProProValProProThrGly 595600605

AspSerGlyAlaProProValProProThrGlyAspSerGlyAlaPro 610615620
ProValProProThrGlyAspSerGlyAlaProProValProProThr 625630635640
GlyAspSerGlyAlaProProValProProThrGlyAspSerGlyAla 645650655
ProProValProProThrGlyAspAlaGlyProProProValProPro 660665670
ThrGlyAspSerGlyAlaProProValProProThrGlyAspSerGly 675680685
AlaProProValThrProThrGlyAspSerGluThrAlaProValPro 690695700
ProThrGlyAspSerGlyAlaProProValProProThrGlyAspSer 705710715720
GluAlaAlaProValProProThrAspAspSerLysGluAlaGlnMet 725730735
ProAlaValIleArgPhe 740 (2) INFORMATION

FOR SEQ ID NO:3: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 3018 base pairs (B) TYPE: nucleic acid

(C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: cDNA (iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO (ix) FEATURE: (A) NAME/KEY: misc. feature (B) LOCATION: 1..742 (D) OTHER

INFORMATION: /Function ="Nucleotides 679 through 2904 encode the amino acid sequence for the

Human Milk Bile Salt- activated Lipase." (xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

CTCAATTGGAGGATCAAAGTTGAGAAAAGTAATATTCGACATTTTT
CGATTCAACGGAGT60

GGCCACCAAGACGATGTCATAGAAGTCTGAACGAGTCTCAGTTCC
AATTTGGTAGACCAC120

TTCATACATCTTTGTTGGATTTCCTGTGTACTTGGTCTTTGTTTTCT
CCTCGATGTACAT180

TACTGAGCCAGATATAAGATTGCTTTTGGATGCCTGCAGAAGCCCT
GAGCAAACAAGTTT240

ATTGCCACCTTCTACTGCCCAAAGGCCAGAATCAGAACAGGACAG
TGACACCGCCCCCAC300

AAAGGCATTGATGTCCGTGCTTTGGCCATAATTGACCCTCATAACA
GGAGCAATCATTTC360

ATTGAGGAACTTCTCAGAAAAGCCGGCCTTTTGCAAGGTTTCAAG
AAGTGTTCGATTAAG420

CATTCCAAGGAAGTCATCTCCTCCTAGAGCATGAAGTAATTTTTCG
ACACTACTGAAGGC480

ATAGTCATGAGACTGGTAGCGGTAGATCCTCATGAACTTGTCTAA
CACGTCCTCTACCCA540

CATGTGCATACGGAGGGATTGAAATCCATAGCGCCAAACTAATTT
AATCACGTTAATTAT600

GAACCAGTTGCTCTCCTCAAATACCAGAGTCTCTCCATTATATATC
CCCAGTAGGCCACC660

CAGAGGCTGATGCTCACCATGGGGCGCCTGCAACTGGTTGTGTTG
GGCCTCACCTGCTGC720

TGGGCAGTGGCGAGTGCCGCGAAGCTGGGCGCCGTGTACACAGA
AGGTGGGTTCGTGGAA780

GGCGTCAATAAGAAGCTCGGCCTCCTGGGTGACTCTGTGGACATC
TTCAAGGGCATCCCC840

TTCGCAGCTCCCACCAAGGCCCTGGAAAATCCTCAGCCACATCCT
GGCTGGCAAGGGACC900

CTGAAGGCCAAGAACTTCAAGAAGAGATGCCTGCAGGCCACCATC
ACCCAGGACAGCACC960

TACGGGGATGAAGACTGCCTGTACCTCAACATTTGGGTGCCCCAG
GGCAGGAAGCAAGTC1020

TCCCGGGACCTGCCCGTTATGATCTGGATCTATGGAGGCGCCTTCC
TCATGGGGTCCGGC1080

CLPR:

5. The method of claim 1 wherein the polypeptide is in combination with a pharmaceutical carrier

acceptable for oral administration.

32. Document ID: US 5681819 A

L10: Entry 32 of 42

File: USPT

Oct 28, 1997

US-PAT-NO: 5681819

DOCUMENT-IDENTIFIER: US 5681819 A

TITLE: Method and compositions for reducing cholesterol absorption

DATE-ISSUED: October 28, 1997

US-CL-CURRENT: 514/12; 514/13, 514/14, 514/15, 514/16, 514/17, 514/18

APPL-NO: 8/ 479160

DATE FILED: June 7, 1995

PARENT-CASE:

BACKGROUND OF THE INVENTION This application is a continuation-in-part of U.S. Ser. No.

08/347,718, filed Dec. 1, 1994.

IN: Tang; Jordan J. N., Wang; Chi-Sun

AB: Compositions derived from all or a portion of the carboxy terminal region of

human bile salt-activated lipase (BAL) are described, which, when orally ingested, compete

with native BAL in binding to the intestinal surface, thus reducing the physiological role

of BAL in mediating the transfer of cholesterol into the intestinal cells, and, as a result,

reducing the amount of cholesterol absorbed from the intestine into the blood stream. Useful

derivatives of the carboxy terminal region of BAL are derived from all or portion of the

region containing amino acid residues 539 to 722, and have a mucin-like structure containing

at least three of the repeating proline-rich units of eleven amino acid residues each.

L10: Entry 32 of 42

File: USPT

Oct 28, 1997

DOCUMENT-IDENTIFIER: US 5681819 A

TITLE: Method and compositions for reducing cholesterol absorption

DEPR:

Pharmaceutical compositions containing C-tail protein, designed to improve the pharmaceutical

activity of the C-tail protein when administered to a patient in an amount effective to reduce

cholesterol uptake in the intestine and thereby decrease blood cholesterol levels, can be

prepared in combination with appropriate pharmaceutical stabilization compounds, delivery

vehicles, carriers, inert diluents, and/or other additives appropriate for enteral (oral)

administration according to methods well known in the art. The formulation usually provides for

release within the stomach or the intestine. The C-tail protein can be formulated into a liquid,

paste, suspension, gel, powders, tablets, capsules, food additives or other standard forms.

Pharmaceutically compatible binding agents and/or adjuvant materials can be included as part of

the composition. Examples include a binder such as microcrystalline cellulose, gum tragacanth, or

gelatin; an excipient such as starch or lactose; a disintegrating agent such as alginic acid,

Primogen.TM., or corn starch; a lubricant such as magnesium stearate or sterotes; aglidant such

as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; and/or a flavoring

agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a

capsule, it can contain, in addition to material of the above type, a liquid carrier. Other

dosage unit forms may further include coatings of sugar, shellac, or other enteric agents. The

C-tail protein can be administered as a component of a fluid such as an elixir, suspension,

beverage, liquid dietary supplement or substitute, or syrup; or of a solid such as a wafer or

candy. The C-tail protein can also be mixed with other active materials that do not impair the

desired action, or with materials that supplement the desired action, such as other blood

lipid-lowering pharmaceutical compositions.

DEPR:

In one preferred embodiment, C-tail protein is encapsulated within carriers that effect release

in the small intestine, such as microparticles, microcapsules, or microspheres prepared from

synthetic or natural polymers such as proteins, polyhydroxy acids, or polysaccharides.

Appropriate systems are known to those skilled in the art. Several microsphere formulations have

been proposed as a means for oral drug delivery. These formulations generally serve to protect

the encapsulated compound and to deliver the compound into the blood stream. Enteric coated

formulations have been widely used for many years to protect drugs administered orally, as well

as to delay release. Other formulations designed to deliver compounds into the blood stream, as

well as to protect the encapsulated drug, are formed of a hydrophobic protein, such as zein, as

described in PCT/US90/06430 and PCT/US90/06433; "proteinoids", as described in U.S. Pat. No.

4,976,968 to Steiner; or synthetic polymers, as described in European Patent application 0 333

523 by the UAB Research Foundation and Southern Research Institute. EPA 0 333 523 described

microparticles of less than ten microns in diameter that contain antigens, for use in oral

administration of vaccines. Larger sizes are preferred for the uses described herein to avoid

uptake into the blood and lymph systems of the encapsulated C-tail protein.

DEPR:

These results indicate that oral administration of the C-tail of BAL, recombinant C-tail and

natural or chemically synthesized C-tail analogs shold be useful to reduce triglyceride

absorption in humans, which should have medical or nutritional benefits.

DETL:

SEQUENCE LISTING (1)

GENERAL INFORMATION: (iii) NUMBER OF SEQUENCES: 6 (2) INFORMATION FOR SEQ ID NO:1: (i) SEQUENCE

CHARACTERISTICS: (A) LENGTH: 722 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii)

MOLECULE TYPE: protein (iii) HYPOTHETICAL: NO (v) FRAGMENT TYPE: internal (xi) SEQUENCE

DESCRIPTION: SEQ ID NO:1:

AlaLysLeuGlyAlaValTyrThrGluGlyGlyPheValGluGlyVal 151015

AsnLysLysLeuGlyLeuLeuGlyAspSerValAspIlePheLysGly 202530

IleProPheAlaAlaProThrLysAlaLeuGluAsnProGlnProHis 354045

ProGlyTrpGlnGlyThrLeuLysAlaLysAsnPheLysLysArgCys 505560

LeuGlnAlaThrIleThrGlnAspSerThrTyrGlyAspGluAspCys 65707580

LeuTyrLeuAsnIleTrpValProGlnGlyArgLysGlnValSerArg 859095

AspLeuProValMetIleTrpIleTyrGlyGlyAlaPheLeuMetGly 100105110

SerGlyHisGlyAlaAsnPheLeuAsnAsnTyrLeuTyrAspGlyGlu 115120125

GluIleAlaThrArgGlyAsnValIleValValThrPheAsnTyrArg 130135140

ValGlyProLeuGlyPheLeuSerThrGlyAspAlaAsnLeuProGly 145150155160

AsnTyrGlyLeuArgAspGlnHisMetAlaIleAlaTrpValLysArg 165170175

AsnIleAlaAlaPheGlyGlyAspProAsnAsnIleThrLeuPheGly 180185190

GluSerAlaGlyGlyAlaSerValSerLeuGlnThrLeuSerProTyr 195200205

AsnLysGlyLeuIleArgArgAlaIleSerGlnSerGlyValAlaLeu 210215220

SerProTrpValIleGlnLysAsnProLeuPheTrpAlaLysLysVal 225230235240

AlaGluLysValGlyCysProValGlyAspAlaAlaArgMetAlaGln 245250255

CysLeuLysValThrAspProArgAlaLeuThrLeuAlaTyrLysVal 260265270

ProLeuAlaGlyLeuGluTyrProMetLeuHisTyrValGlyPheVal 275280285

ProValIleAspGlyAspPheIleProAlaAspProIleAsnLeuTyr 290295300

AlaAsnAlaAlaAspIleAspTyrIleAlaGlyThrAsnAsnMetAsp 305310315320

GlyHisIlePheAlaSerIleAspMetProAlaIleAsnLysGlyAsn 325330335

LysLysValThrGluGluAspPheTyrLysLeuValSerGluPheThr 340345350

IleThrLysGlyLeuArgGlyAlaLysThrThrPheAspValTyrThr 355360365

GluSerTrpAlaGlnAspProSerGlnGluAsnLysLysLysThrVal 370375380

ValAspPheGluThrAspValLeuPheLeuValProThrGluIleAla 385390395400

LeuAlaGlnHisArgAlaAsnAlaLysSerAlaLysThrTyrAlaTyr 405410415

LeuPheSerHisProSerArgMetProValTyrProLysTrpValGly 420425430

AlaAspHisAlaAspAspIleGlnTyrValPheGlyLysProPheAla 435440445

ThrProThrGlyTyrArgProGlnAspArgThrValSerLysAlaMet 450455460

IleAlaTyrTrpThrAsnPheAlaLysThrGlyAspProAsnMetGly 465470475480

AspSerAlaValProThrHisTrpGluProTyrThrThrGluAsnSer 485490495

GlyTyrLeuGluIleThrLysLysMetGlySerSerSerMetLysArg 500505510

SerLeuArgThrAsnPheLeuArgTyrTrpThrLeuThrTyrLeuAla 515520525

LeuProThrValThrAspGlnGluAlaThrProValProProThrGly 530535540

AspSerGluAlaThrProValProProThrGlyAspSerGluThrAla 545550555560

ProValProProThrGlyAspSerGlyAlaProProValProProThr 565570575

GlyAspSerGlyAlaProProValProProThrGlyAspSerGlyAla 580585590

ProProValProProThrGlyAspSerGlyAlaProProValProPro 595600605

ThrGlyAspSerGlyAlaProProValProProThrGlyAspSerGly 610615620

AlaProProValProProThrGlyAspSerGlyAlaProProValPro 625630635640

ProThrGlyAspAlaGlyProProProValProProThrGlyAspSer 645650655

GlyAlaProProValProProThrGlyAspSerGlyAlaProProVal 660665670

ThrProThrGlyAspSerGluThrAlaProValProProThrGlyAsp 675680685

SerGlyAlaProProValProProThrGlyAspSerGluAlaAlaPro 690695700

ValProProThrAspAspSerLysGluAlaGlnMetProAlaValIle 705710715720

ArgPhe (2) INFORMATION FOR SEQ ID

NO:2: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 742 amino acids (B) TYPE: amino acid (D)

TOPOLOGY: linear (ii) MOLECULE TYPE: protein (iii) HYPOTHETICAL: NO (v) FRAGMENT TYPE: internal

(ix) FEATURE: (A) NAME/KEY: Modified-site (B) LOCATION: 186..187 (D) OTHER INFORMATION: /note=

"Position 187 represents a potential N- linked glycosylation site." (ix) FEATURE: (A) NAME/KEY:

Modified-site (B) LOCATION: 193..194 (D) OTHER INFORMATION: /note= "The serine at position 194

represents an active site serine." (ix) FEATURE: (A) NAME/KEY: misc. feature (B) LOCATION: 1..742

(D) OTHER INFORMATION: /Function = "Amino acid sequence for the Human Milk Bile Salt-activated

Lipase." (xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

MetGlyArgLeuGlnLeuValValLeuGlyLeuThrCysCysTrpAla

151015 ValAlaSerAlaAlaLysLeuGlyAlaValTyrThrGluGlyGlyPhe 202530

ValGluGlyValAsnLysLysLeuGlyLeuLeuGlyAspSerValAsp 354045

IlePheLysGlyIleProPheAlaAlaProThrLysAlaLeuGluAsn 505560

ProGlnProHisProGlyTrpGlnGlyThrLeuLysAlaLysAsnPhe 65707580

LysLysArgCysLeuGlnAlaThrIleThrGlnAspSerThrTyrGly 859095

AspGluAspCysLeuTyrLeuAsnIleTrpValProGlnGlyArgLys 100105110

GlnValSerArgAspLeuProValMetIleTrpIleTyrGlyGlyAla 115120125

PheLeuMetGlySerGlyHisGlyAlaAsnPheLeuAsnAsnTyrLeu 130135140

TyrAspGlyGluGluIleAlaThrArgGlyAsnValIleValValThr 145150155160

PheAsnTyrArgValGlyProLeuGlyPheLeuSerThrGlyAspAla 165170175

AsnLeuProGlyAsnTyrGlyLeuArgAspGlnHisMetAlaIleAla 180185190

TrpValLysArgAsnIleAlaAlaPheGlyGlyAspProAsnAsnIle 195200205

ThrLeuPheGlyGluSerAlaGlyGlyAlaSerValSerLeuGlnThr 210215220

LeuSerProTyrAsnLysGlyLeuIleArgArgAlaIleSerGlnSer 225230235240

GlyValAlaLeuSerProTrpValIleGlnLysAsnProLeuPheTrp 245250255

AlaLysLysValAlaGluLysValGlyCysProValGlyAspAlaAla 260265270

ArgMetAlaGlnCysLeuLysValThrAspProArgAlaLeuThrLeu 275280285

AlaTyrLysValProLeuAlaGlyLeuGluTyrProMetLeuHisTyr 290295300

ValGlyPheValProValIleAspGlyAspPheIleProAlaAspPro 305310315320

IleAsnLeuTyrAlaAsnAlaAlaAspIleAspTyrIleAlaGlyThr 325330335

AsnAsnMetAspGlyHisIlePheAlaSerIleAspMetProAlaIle 340345350

AsnLysGlyAsnLysLysValThrGluGluAspPheTyrLysLeuVal 355360365
SerGluPheThrIleThrLysGlyLeuArgGlyAlaLysThrThrPhe 370375380
AspValTyrThrGluSerTrpAlaGlnAspProSerGlnGluAsnLys 385390395400
LysLysThrValValAspPheGluThrAspValLeuPheLeuValPro 405410415
ThrGluIleAlaLeuAlaGlnHisArgAlaAsnAlaLysSerAlaLys 420425430
ThrTyrAlaTyrLeuPheSerHisProSerArgMetProValTyrPro 435440445
LysTrpValGlyAlaAspHisAlaAspAspIleGlnTyrValPheGly 450455460
LysProPheAlaThrProThrGlyTyrArgProGlnAspArgThrVal 465470475480
SerLysAlaMetIleAlaTyrTrpThrAsnPheAlaLysThrGlyAsp 485490495
ProAsnMetGlyAspSerAlaValProThrHisTrpGluProTyrThr 500505510
ThrGluAsnSerGlyTyrLeuGluIleThrLysLysMetGlySerSer 515520525
SerMetLysArgSerLeuArgThrAsnPheLeuArgTyrTrpThrLeu 530535540
ThrTyrLeuAlaLeuProThrValThrAspGlnGluAlaThrProVal 545550555560
ProProThrGlyAspSerGluAlaThrProValProProThrGlyAsp 565570575
SerGluThrAlaProValProProThrGlyAspSerGlyAlaProPro 580585590
ValProProThrGlyAspSerGlyAlaProProValProProThrGly 595600605
AspSerGlyAlaProProValProProThrGlyAspSerGlyAlaPro 610615620
ProValProProThrGlyAspSerGlyAlaProProValProProThr 625630635640
GlyAspSerGlyAlaProProValProProThrGlyAspSerGlyAla 645650655
ProProValProProThrGlyAspAlaGlyProProProValProPro 660665670
ThrGlyAspSerGlyAlaProProValProProThrGlyAspSerGly 675680685
AlaProProValThrProThrGlyAspSerGluThrAlaProValPro 690695700
ProThrGlyAspSerGlyAlaProProValProProThrGlyAspSer 705710715720
GluAlaAlaProValProProThrAspAspSerLysGluAlaGlnMet 725730735
ProAlaValIleArgPhe 740 (2) INFORMATION
FOR SEQ ID NO:3: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 3018 base pairs (B) TYPE: nucleic acid
(C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: cDNA (iii) HYPOTHETICAL: NO
(iv) ANTI-SENSE: NO (ix) FEATURE: (A) NAME/KEY: misc. feature (B) LOCATION: 1..742 (D) OTHER
INFORMATION: /Function = "Nucleotides 679 through 2904 encode the amino acid sequence for the
Human Milk Bile Salt- activated Lipase." (xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

CTCAATTGGAGGATCAAAGTTGAGAAAAGTAATATTCGACATTTTT
CGATTCAACGGAGT60

GGCCACCAAGACGATGTCATAGAAGTCTGAACGAGTCTCAGTTCC
AATTTGGTAGACCAC120

TTCATACATCTTTGTTGGATTTCCTGTGTACTTGGTCTTTGTTTTCT
CCTCGATGTACAT180

TACTGAGCCAGATATAAGATTGCTTTTGGATGCCTGCAGAAGCCCT
GAGCAAACAAGTTT240

ATTGCCACCTTCTACTGCCCAAAGGCCAGAATCAGAACAGGACAG
TGACACCGCCCCCAC300

AAAGGCATTGATGTCCGTGCTTTGGCCATAATTGACCCTCATAACA
GGAGCAATCATTTC360

ATTGAGGAACTTCTCAGAAAAGCCGGCCTTTTGCAAGGTTTCAAG
AAGTGTTCGATTAAG420

CATTCCAAGGAAGTCATCTCCTCCTAGAGCATGAAGTAATTTTTCG
ACACTACTGAAGGC480

ATAGTCATGAGACTGGTAGCGGTAGATCCTCATGAACTTGTCTAA
CACGTCCTCTACCCA540

CATGTGCATACGGAGGGATTGAAATCCATAGCGCCAAACTAATTT
AATCACGTTAATTAT600

GAACCAGTTGCTCTCCTCAAATACCAGAGTCTCTCCATTATATATC
CCCAGTAGGCCACC660

CAGAGGCTGATGCTCACCATGGGGCGCCTGCAACTGGTTGTGTTG
GGCCTCACCTGCTGC720

TGGGCAGTGGCGAGTGCCGCGAAGCTGGGCGCCGTGTACACAGA
AGGTGGGTTCGTGGAA780

GGCGTCAATAAGAAGCTCGGCCTCCTGGGTGACTCTGTGGACATC
TTCAAGGGCATCCCC840

TTCGCAGCTCCCACCAAGGCCCTGGAAAATCCTCAGCCACATCCT
GGCTGGCAAGGGACC900

CTGAAGGCCAAGAACTTCAAGAAGAGATGCCTGCAGGCCACCATC
ACCCAGGACAGCACC960

TACGGGGATGAAGACTGCCTGTACCTCAACATTTGGGTGCCCCAG
GGCAGGAAGCAAGTC1020

TCCCGGGACCTGCCCGTTATGATCTGGATCTATGGAGGCGCCTTCC
TCATGGGGTCCGGC1080

CLPR:
1. A composition for reducing intestinal absorption of cholesterol comprising a polypeptide
comprising at least four eleven amino acid repeats having at least three prolines present in the
carboxy terminal region of human bile salt-activated lipase as shown in Sequence ID No. 1, that
binds to a specific receptor on intestinal cells, wherein the polypeptide cannot hydrolyze
cholesterol ester and is in an amount effective to reduce cholesterol uptake into the intestinal
endothelium cells, in combination with a pharmaceutical carrier acceptable for oral
administration.

CLPR:
7. The composition of claim 1 wherein the polypeptide is in a dietary formulation for oral
administration.

33. Document ID: US 5658758 A

L10: Entry 33 of 42

File: USPT

Aug 19, 1997

US-PAT-NO: 5658758
DOCUMENT-IDENTIFIER: US 5658758 A
TITLE: Polynucleotides encoding cytostatin I
DATE-ISSUED: August 19, 1997

US-CL-CURRENT: 435/69.1; 435/252.3, 435/320.1, 435/325, 435/348, 435/358, 435/365, 435/419,
435/466, 435/70.1, 536/23.1 , 536/23.5

APPL-NO: 8/ 409731
DATE FILED: March 24, 1995

IN: Ni; Jian, Gentz; Reiner, Yu; Guo-Liang, Rosen; Craig A.

AB: A human cytostatin I polypeptide and DNA encoding such polypeptide and a
procedure for producing such polypeptide by recombinant techniques is disclosed. Also
disclosed are methods for utilizing such polypeptide for the treatment of cancers,
particularly breast cancer, leukemias, and other matastases.

L10: Entry 33 of 42

File: USPT

Aug 19, 1997

DOCUMENT-IDENTIFIER: US 5658758 A
TITLE: Polynucleotides encoding cytostatin I

BSPR:
Peptides that locally signal growth cessation and stimulate differentiation of the developing
epithelium are very important for mammary gland development. Recombinant and wild-type forms of
mammary-derived growth inhibitor (MDGI) and heart-fatty acid binding protein (FABP), which belong
to the FABP family, specifically inhibit growth of normal mouse mammary epithelial cells (MEC)
and promote morphological differentiation, stimulates its own expression and promotes milk
protein synthesis. Selective inhibition of endogenous MDGI expression in MEC by antisense
phosphorothioate oligonucleotides suppresses appearance of alveolar end buds and lowers the beta-
casein level in organ cultures. Furthermore, MDGI suppresses the mitogenic effects of EGF, and
EGF antagonizes the activities of MDGI. Finally, the regulatory properties of MDGI can be fully
mimicked by an 11-amino acid sequence, represented in the COOH terminus of MDGI and a subfamily
of structurally related FABPs. MDGI is the first known growth inhibitor which promotes mammary
gland differentiation. The amount of MDGI increased dramatically with the onset of lactation
after delivery. Recent studies shows that a new posttranslational processing form of MDGI, MDGI
2, not present in lactation, was found in the bovine gland during pregnancy.(Brandt et al,
Biochem Biophy Res Comm Vol 189, p406, Nov. 30, 1992) To date, bovine, rat and mouse MDGI have
been identified but no human MDGI or MDGI-like protein.

DRPR:
The pharmaceutical compositions may be administered in a convenient manner such as by the oral
(when protected from hydrolysis or digestion), topical, intravenous, intraperitoneal,
intramuscular, subcutaneous, intranasal or intradermal routes. The pharmaceutical compositions
are administered in an amount which is effective for treating and/or prophylaxis of the specific
indication. In general, they are administered in an amount of at least about 10 .mu.g/kg body
weight and in most cases they will be administered in an amount not in excess of about 8 mg/Kg
body weight per day. In most cases, the dosage is from about 10 .mu.g/kg to about 1 mg/kg body
weight daily, taking into account the routes of administration, symptoms, etc.

34. Document ID: US 5618809 A

L10: Entry 34 of 42

File: USPT

Apr 8, 1997

US-PAT-NO: 5618809
DOCUMENT-IDENTIFIER: US 5618809 A
TITLE: Indolocarbazoles from saccharothrix aerocolonigenes copiosa subsp. nov SCC 1951 ATCC 53856
DATE-ISSUED: April 8, 1997

US-CL-CURRENT: 514/211.08; 514/410, 540/545, 548/416

APPL-NO: 8/ 394937
DATE FILED: February 27, 1995

PARENT-CASE:
CROSS-REFERENCE TO RELATED APPLICATION This is a continuation of application Ser. No. 07/451,487, filed Dec. 14, 1989, abandoned. This application is related to a commonly-owned invention by the
same inventors U.S. patent application Ser. No. 07/451,271, filed Dec. 14, 1989 which is directed
to N-alkanoylstaurosporine derivatives, especially-N-acetylstaurospodne which are isolated from
Saccharothrix aerocolonigenes subsp. copiosa subsp. nov. SCC 1951, ATCC 53856.

IN: Barrabee; Ellen B., Horan; Ann C., Gentile; Frank A., Patel; Mahesh G.

AB: N-alkanoyl derivatives of staurospodne represented by the formula I ##STR1##
wherein R.sub.a and R.sub.b are each H or ##STR2## wherein R.sub.1 and R.sub.2 are
independently H or --OH or --OCH.sub.3 and R.sub.3 is OH, NHCH.sub.3, NCH COCH.sub.3 or
NHCOCH.sub.3 and R.sub.4 is OH or H and, stereochemical isomers thereof with the provisos
that (1) when R.sub.a and R.sub.b .dbd.A, and R.sub.1.dbd.H.sub.2 or OH R.sub.3 is not
NHCH.sub.3 ; (2) when R.sub.a and R.sub.b.dbd. B, then R.sub.1 .dbd.R.sub.4 .dbd.OH or
R.sub.1 .dbd.R.sub.4 .dbd.H; (3) when R.sub.a .dbd.R.sub.b .dbd.H R.sub.1 .dbd.--OCH.sub.3,
and (4) when R.sub.a and R.sub.b .dbd.A, and R.sub.1 .dbd.H and R.sub.2 .dbd.OCH.sub.3, then
R3 is not and ##STR3## pharmaceutical compositions thereof useful for inhibiting myosin
light chain kinase, protein kinase C or tumor cell proliferation as well as producing an
antihypertensive effect and an anti-inflammatory effect in warm-blood animals such as man
are disclosed.

L10: Entry 34 of 42

File: USPT

Apr 8, 1997

DOCUMENT-IDENTIFIER: US 5618809 A
TITLE: Indolocarbazoles from saccharothrix aerocolonigenes copiosa subsp. nov SCC 1951 ATCC 53856

DEPR:
Purified cell wall preparations of SCC 1951 analyzed by the method of Becker [Becker et. al.,
Appl., Microbiol. 12, 421-423 (1964)] contain the meso-isomer of 2,-6-diaminopimelic acid,
alanine, glutamic acid, glucosamine, muramic acid and galactose (Type III). Whole-cell
hydrolysates analyzed by the method of Lechevalier [Lechevalier, M. P., J. Lab. Clin. Med. 71,
934-944 (1968)] contain galactose, glucose, mannose, ribose, rhamnose and a trace of madurose.
The phospholipids present are diphosphatidylglycerol, phosphatidylinositol, phosphatidylinositol
mannosides, phosphatidylethanolamine acylated to both hydroxy and branched chain fatty acids and
a minor unknown (Type PII). [Lechevalier et al., Biochem. System. Ecol. 5, 249-260 (1977)]. No
mycolates are present. The mole % guanine plus cytosine of the DNA is 71.2% (Tm).

DEPR:
Examples of suitable pharmaceutical compositions include solid compositions for oral
administration such as tablets, capsules, pills, powders and granules, liquid compositions for
oral administration such as solutions, suspensions or emulsions. They may also be manufactured in
the form of sterile solid compositions which can be dissolved in sterile water, physiological
saline or some other sterile injectable medium immediately before use.

35. Document ID: US 5571536 A

L10: Entry 35 of 42

File: USPT

Nov 5, 1996

US-PAT-NO: 5571536
DOCUMENT-IDENTIFIER: US 5571536 A
TITLE: Formulations of compounds as nanoparticulate dispersions in digestible oils or fatty acids
DATE-ISSUED: November 5, 1996

US-CL-CURRENT: 424/489; 424/450, 424/495, 424/498, 424/499, 514/772.1, 514/937, 514/938, 514/951

APPL-NO: 8/ 384057
DATE FILED: February 6, 1995

IN: Eickhoff; W. Mark, Mueller; Karl R., Engers; David A.

AB: Nanoparticulate crystalline drug substances formulated in an aqueos phase
emulsified in oil, are able to be made at less than 1000 nm size and provide increased
bioavailability and lymphatic uptake following oral administration.

L10: Entry 35 of 42

File: USPT

Nov 5, 1996

DOCUMENT-IDENTIFIER: US 5571536 A
TITLE: Formulations of compounds as nanoparticulate dispersions in digestible oils or fatty acids

ABPL:
Nanoparticulate crystalline drug substances formulated in an aqueos phase emulsified in oil, are
able to be made at less than 1000 nm size and provide increased bioavailability and lymphatic
uptake following oral administration.

BSPR:
The present invention relates to formulations of compounds as nanoparticulate aqueous dispersions
emulsified in digestible oils or fatty acids with or without additional stabilizers. More
particularly, the present invention increases the bioavailability of phamacological compounds and
allows pharmacological compounds to be delivered directly to the lymphatic systems following oral
administration.

BSPR:
Intestinal lymphatic uptake has long been proposed as a route for drugs to increase systemic
bioavailability by avoiding first pass metabolism and hepobiliary elimination pathways following
oral administration. However, no strong data in the literature exists which suggest there is an
oral delivery system which actually can target this absorption pathway to any great extent.
Formulation of drugs in oils and fatty acids is a traditional approach which has shown some
success, but is by no means predictable. These approaches have focused on compounds with high log
P and high lipid solubility, and even under these conditions results have been mixed. This
approach suffers from the limitation that most compounds have limited solubility in digestible
oils or fatty acids to the extent that development into a solid dosage form is not practical,
that is, too large a capsule is needed to provide the dose.

BSPR:
The present invention provides improved oral bioavailability for any compound which possesses
extensive first pass elimination and that can be formulated as a nanoparticulate in a digestible
oil or fatty acid. It is theorized that nanoparticles are rapidly carried intact into the
intestinal lymphatic ducts/vessels via the lipid transport pathway where subsequent dissolution
in lymph/blood partitioning occurs. Eventually, any undissolved nanoparticulate will drain into
the systemic circulation and represent a late phase delivery pathway.

DEPR:
The present invention is based on the hypothesis that oral bioavailability can be dramatically
improved for any compound which possesses extensive first pass elimination and that can be
formulated as a nanoparticulate in a digestible oil or fatty acid.

DEPR:
The present invention can be practiced with a wide variety of crystalline materials that are
water insoluble or poorly soluble in water. As used herein, poorly soluble means that the
material has a solubility in aqueous medium of less than about 10 mg/ml, and preferably of less
than about 1 mg/ml. Examples of the preferred crystalline material are as follows. The
therapeutic candidates include
[6-methoxy-4-(1-methylethyl)-3-oxo-1,2-benzisothiazol-2-(3H)-yl]
methyl 2,6-dichlorobenzoate, S,S-dioxide, described in U.S. Pat. No. 5,128,339 (WIN 63394),
closporin, propanolol, antifungals, antivirals, themetherapeutics, oligonucleotides, peptides or
peptidomimetics and proteins. In addition it is believed that vaccines can also be delivered to
the lymphatic system by use of the present invention. The present invention also allows imaging
of the intestinal lymphatic system with X-ray or MRI agents formulated as nanoparticles in
digestible oils or fatty acids. Potential imaging agents include any X-ray or MRI nanoparticulate
core.

36. Document ID: US 5560931 A

L10: Entry 36 of 42

File: USPT

Oct 1, 1996

US-PAT-NO: 5560931
DOCUMENT-IDENTIFIER: US 5560931 A
TITLE: Formulations of compounds as nanoparticulate dispersions in digestible oils or fatty acids
DATE-ISSUED: October 1, 1996

US-CL-CURRENT: 424/489; 424/498, 514/937, 514/938, 514/939, 514/943

APPL-NO: 8/ 388088
DATE FILED: February 14, 1995

IN: Eickhoff; W. Mark, Mueller; Karl R., Engers; David A.

AB: Nanoparticulate crystalline drug substances formulated in an aqueos phase
emulsified in oil, are able to be made at less than 1000 nm size and provide increased
bioavailability and lymphatic uptake following oral administration.

L10: Entry 36 of 42

File: USPT

Oct 1, 1996

DOCUMENT-IDENTIFIER: US 5560931 A
TITLE: Formulations of compounds as nanoparticulate dispersions in digestible oils or fatty acids

ABPL:
Nanoparticulate crystalline drug substances formulated in an aqueos phase emulsified in oil, are
able to be made at less than 1000 nm size and provide increased bioavailability and lymphatic
uptake following oral administration.

BSPR:
The present invention relates to formulations of compounds as nanoparticulate aqueous dispersions
emulsified in digestible oils or fatty acids with or without additional stabilizers. More
particularly, the present invention increases the bioavailability of phamacological compounds and
allows pharmacological compounds to be delivered directly to the lymphatic systems following oral
administration.

BSPR:
Intestinal lymphatic uptake has long been proposed as a route for drugs to increase systemic
bioavailability by avoiding first pass metabolism and hepobiliary elimination pathways following
oral administration. However, no strong data in the literature exists which suggest there is an
oral delivery system which actually can target this absorption pathway to any great extent.
Formulation of drugs in oils and fatty acids is a traditional approach which has shown some
success, but is by no means predictable. These approaches have focused on compounds with high log
P and high lipid solubility, and even under these conditions results have been mixed. This
approach suffers from the limitation that most compounds have limited solubility in digestible
oils or fatty acids to the extent that development into a solid dosage form is not practical,
that is, too large a capsule is needed to provide the dose.

BSPR:
The present invention provides improved oral bioavailability for any compound which possesses
extensive first pass elimination and that can be formulated as a nanoparticulate in a digestible
oil or fatty acid. It is theorized that nanoparticles are rapidly carried intact into the
intestinal lymphatic ducts/vessels via the lipid transport pathway where subsequent dissolution
in lymph/blood partitioning occurs. Eventually, any undissolved nanoparticulate will drain into
the systemic circulation and represent a late phase delivery pathway.

BSPR:
The present invention is based on the hypothesis that oral bioavailability can be dramatically
improved for any compound which possesses extensive first pass elimination and that can be
formulated as a nanoparticulate in a digestible oil or fatty acid.

BSPR:
The present invention can be practiced with a wide variety of crystalline materials that are
water insoluble or poorly soluble in water. As used herein, poorly soluble means that the
material has a solubility in aqueous medium of less than about 10 mg/ml, and preferably of less
than about 1 mg/ml. Examples of the preferred crystalline material are as follows. The
therapeutic candidates include [6-methoxy-4-(1-methylethyl)-3-oxo-1,2-benzisothiazol-2(3H)-yl]
methyl 2,6-dichlorobenzoate, S,S-dioxide, described in U.S. Pat. No. 5,128,339 (WIN 63394),
cyclosporin, propanolol, antifungals, antivirals, chemotherapeutics, oligonucleotides, peptides
or peptidomimetics and proteins. In addition it is believed that vaccines can also be delivered
to the lymphatic system by use of the present invention. The present invention also allows
imaging of the intestinal lymphatic system with X-ray or MRI agents formulated as nanoparticles
in digestible oils or fatty acids. Potential imaging agents include any X-ray or MRI
nanoparticulate core.

37. Document ID: US 5521061 A

L10: Entry 37 of 42

File: USPT

May 28, 1996

US-PAT-NO: 5521061
DOCUMENT-IDENTIFIER: US 5521061 A
TITLE: Enhancement of probe signal in nucleic acid-mediated in-situ hybridization studies
DATE-ISSUED: May 28, 1996

US-CL-CURRENT: 435/5; 435/6, 435/7.1, 435/7.2, 435/7.92, 435/810, 436/501, 436/63, 536/22.1,
536/23.1, 536/24.1

APPL-NO: 7/916068
DATE FILED: July 17, 1992

IN: Bresser; Joel, Cubbage; Michael L., Prashad; Nagindra, Weber; William D., Chen
Ju; Shyh

AB: Solutions useful for hybridizing cells and viruses with nucleic acid and antibody
probes, their usefulness increased due to the presence of permeation enhancers and signal
enhancers, including permeation enhancers; also the hybridization processes wherein the
solutions are used.

L10: Entry 37 of 42

File: USPT

May 28, 1996

DOCUMENT-IDENTIFIER: US 5521061 A
TITLE: Enhancement of probe signal in nucleic acid-mediated in-situ hybridization studies

DEPR:
In a preferred embodiment of the permeation enhancer-modified process, wherein the target
molecule is a nucleic acid molecule, the assay solution comprises a nucleic acid probe and DMSO

(2 to 20 percent) and one or more compounds selected from the group, an alcohol (2 to 20
percent), an aliphatic alkane (2 to 20 percent), an alkene (2 to 20 percent), a cyclodextrin (2
to 20 percent), a fatty acid ester (2 to 20 percent) of the formula R.sub.1 (COO)R.sub.2, an
amide or lactam (2 to 15 percent) of the formula R.sub.3 (NH)(CO)R.sub.4, and an organic silane
(2 to 20 percent) of the formula (SiR.sub.5 R.sub.6 R.sub.7)N(SiR.sub.8 R.sub.9 R.sub.10),
(SiR.sub.5 R.sub.6 R.sub.7)—(SiR.sub.8 R.sub.9 R.sub.10), (SiR.sub.5 R.sub.6 R.sub.7)O(SiR.sub.8
R.sub.9 R.sub.10), or (SiR.sub.5 R.sub.6 O)(SiR.sub.7 R.sub.8 O)(SiR.sub.9 R.sub.10 O) and the
combined volumes of DMSO and the compounds selected from the group not being more than 30 percent
of the assay solution (v/v).

DEPR:
In a combination aspect of the permeation enhancer-modified process, the assay solution comprises
a nucleic acid probe and DMSO (2 to 20 percent) and one or more compounds selected from the
group, an alcohol (2 to 20 percent), an aliphatic alkane (2 to 20 percent), an alkene (2 to 20
percent), a cyclodextrin (2 to 20 percent), a fatty acid ester (2 to 20 percent) of the formula
R.sub.1 (COO)R.sub.2, an amide or lactam (2 to 15 percent) of the formula R.sub.3
(NH)(CO)R.sub.4, and an organic silane (2 to 20 percent) of the formula (SiR.sub.5 R.sub.6
R.sub.7)N(SiR.sub.8 R.sub.9 R.sub.10), (SiR.sub.5 R.sub.6 R.sub.7)—(SiR.sub.8 R.sub.9 R.sub.10),
(SiR.sub.5 R.sub.6 R.sub.7)O(SiR.sub.8 R.sub.9 R.sub.10), or (SiR.sub.5 R.sub.6 O)(SiR.sub.7
R.sub.8 O)(SiR.sub.9 R.sub.10 O), the combined volumes of DMSO and the compounds selected from
the group not being more than 30 percent of the assay solution (v/v).

DEPR:
The amount of Triton in the assay solution will preferably be about 10% The cells can come from
solid tissue (e.g., nerves, muscle, heart, skin, lungs, kidneys, pancreas, spleen, lymph nodes,
testes, cervix, and brain) or cells present in membranes lining various tracts, conduits and
cavities (such as the gastrointestinal tract, urinary tract, vas deferens, uterine cavity,
uterine tube, vagina, respiratory tract, nasal cavity, oral cavity, pharynx, larynx, trachea,
bronchi and lungs) or cells in an organism's fluids (e.g., urine, stomach fluid, sputum, blood
and lymph fluid) or stool.

38. Document ID: US 5464820 A

L10: Entry 38 of 42

File: USPT

Nov 7, 1995

US-PAT-NO: 5464820
DOCUMENT-IDENTIFIER: US 5464820 A
TITLE: Specific inhibitors of tissue kallikrein
DATE-ISSUED: November 7, 1995

US-CL-CURRENT: 514/16; 514/17, 514/18, 530/329, 530/331

APPL-NO: 8/ 079812
DATE FILED: June 22, 1993

IN: Burton; James, Dong; Zhengxin, Frigo; Timothy B.

AB: The invention is directed to substrate analogs which are specific for tissue
kallikrein. These analogs contain a sequence which corresponds to at least positions 388 to
390 of human kininogen, and which has a 4-aminophenylalanine (Phe(4NH.sub.2)), or a
structurally or functionally similar residue, corresponding to position 389. These substrate
analogs are useful in compositions and methods for the treatment or prevention of biological
activities associated with tissue kallikrein including inflammation, the regulation of blood
flow, the regulation of proenzyme activity through processing, shock, hypotension, vascular
leakage, and the perception of pain.

L10: Entry 38 of 42

File: USPT

Nov 7, 1995

DOCUMENT-IDENTIFIER: US 5464820 A
TITLE: Specific inhibitors of tissue kallikrein

DEPR:
Modified amino acids include derivatives and analogs of naturally and non-naturally occurring,
and synthetically produced amino acids. Such amino acid forms have been chemically modified such
as, for example, by halogenation of one or more active sites with chlorine (Cl), bromine (Br),
fluorine (F), or iodine (I), alkylation with a carbon containing group such as a methyl (Me),
ethyl (Et), butyl (Bu), amino (NH.sub.2 or NH.sub.3), amidino (Am), acetomidomethyl (Acm), or
phenyl (Ph) group, or by the addition of a phosphorous (P), nitrogen (N), oxygen (O) or sulfur
(S) containing group. Modifications may also be made by, for example, hydration, oxidation,
hydrogenation, esterification, or cyclization of another amino acid or peptide, or of a precursor
chemical. Examples include the amino acid hydroxamates and decarboxylases, the dansyl amino
acids, the polyamino acids, and amino acid derivatives. Specific examples include gamma amino
butyric acid (GABA), hydroxyproline (Hyp), aminoadipic acid (Aad) which may be modified at the 2
or 3 position, o-aminobutyric acid (Aab or Abu), selenocysteine (SeCys.sub.2), tert-butylglycine
(Bug or tert-BuGly), the N-carbamyl amino acids, the amino acid methyl esters, amino-propionic
acid (or .beta.-alanine; 13-Ala), adamentylglycine (Adg), aminocaproic acid (Acp),
N-ethylasparagine (Et-Asn), allo-hydroxylysine (aHyl), allo-isoleucine (alle), phenylglycine
(Phg), pyridylalanine (Pal), thienylalanine (Thi),
.alpha.-.DELTA.-aminobutyric acid (Kbu),
.alpha.-.beta.-diaminopropionic acid (Kpr), 1- or 2-naptithylalanine (1Nal or 2Nal),
orthofluorophenylalanine (Phe(o-F)), N-methylglycine (MeGly), N-methyl-isoleucine (Melle),
N-methyl-valine (MeVal), 2-amino-heptanoic acid (Ahe), 2- or 3-amino-isobutyric acid (Aib),
2-amino-pimellic acid (Dbu), 2-2'-diaminopimellic acid (Dpm), 2,3-diaminopropionic acid (Dpr),
and N-ethylglycine (EtGly). Chemically produced non-coded amino acids include, for example,
phenylglycine (Ph-Gly), cyclohexylalanine (Cha), cyclohexylglycine (Chg), and 4-amino
phenylalanine (Phe(4NH.sub.2) or Aph). Modified amino acids may also be chemical structures which
are not amino acids at all, but are actually classified as another chemical form such as an alkyl
amine, a saccharide, a nucleic acid, a lipid, a fatty acid or another acid. Any of the modified

or unmodified amino acids which comprise the peptide may be in the D- or L-conformations or
comprise one, two or more tautomeric or resonance forms. All amino acids disclosed herein are in
the L-conformation unless otherwise indicated.

DEPR:
Still another embodiment of the invention is directed to methods for the prevention or treatment
of biological or physiological affects which can be attributed, at least in part, to the activity
of tissue kallikrein. Compositions containing therapeutically or prophylactically effective
amounts of substrate analogs of tissue kallikrein comprising the above-described peptides and can
be administered to a patient which is preferably a human. Effective amounts of a composition are
those amounts which are necessary to alleviate conditions or symptoms produced by the disease or
disorder. Compositions of the invention may be administered to a patient orally, parenterally,
sublingually, rectally, enterally, by pulmonary absorption, or by topical application. Parenteral
injections may be intraperitoneal, intravenous, subcutaneous, intramuscular, intrathecal,
intra-arterially, or by a medi-port system. Preferably the administration is oral.

DEPR:
Bradykinin is also one of the physiological mediators of anaphylaxis. It is released from
cytotoxic antibody-coated mast cells following reaction with an antigen specific for the
antibody. Compositions of specific kallikrein inhibitors would be useful to alleviate conditions
associated with rhinitis, such as vascular permeability of the sinuses. Compositions could be
administered systemically such as by oral formulation, or locally such as by spraying directly
into the sinuses.

39. Document ID: US 5314820 A

L10: Entry 39 of 42

File: USPT

May 24, 1994

US-PAT-NO: 5314820
DOCUMENT-IDENTIFIER: US 5314820 A
TITLE: Process and microorganisms for producing single cell protein
DATE-ISSUED: May 24, 1994

US-CL-CURRENT: 435/252.1; 435/252.4, 435/71.2, 435/804

APPL-NO: 7/ 120322
DATE FILED: November 13, 1987

IN: Hamdan; Ibrahim Y., ElNawawy; Amin S., Banat; Ibrahim M., Al-Awadhi; Nader M.

AB: A methanol-utilizing bacterium selected from the group consisting of
Methylophilus KISRI 5 (NCIB 12135), Methylophilus KISRI 6.1 (NCIB 12136), Methylophilus
KISRI 512 (NCIB 12137), Methylophilus KISRI 5112 (NCIB 12138) and mutants and variants
thereof. Also, bacterial cultures comprising these novel strains of Methylophilus and a
method of producing single cell protein comprising culturing one or more of the
Methylophilus strains of the invention in a methanol-containing aqueous culture medium,
preferably in the culture medium of the invention which has been optimized for culturing
these novel Methylophilus strains. The culture method preferably further comprises the
recycling of spent culture medium.

L10: Entry 39 of 42

File: USPT

May 24, 1994

DOCUMENT-IDENTIFIER: US 5314820 A
TITLE: Process and microorganisms for producing single cell protein

DEPR:
Each culture was subjected to a large number of tests typical of those used for identifying new
and existing strains of bacteria, including: morphological (4); cultural (14); sugar fermentation
(17); nitrogen source utilization (8); carbon source assimilation (71); enzyme activity (19);
biochemical (16); antibiotic sensitivity (21); specific media growth (7); growth at different pH
(6); and growth at different temperatures (6) (the numbers in brackets are the number of the
different tests carried out in eachcategory). In addition to these conventional tests, the new
cultures were also characterized with respect to their polar lipids, their deoxyribonucleic acid
(DNA) base ratio values (mole percent of guanine plus cytosine) and their straight chain fatty
acid composition.

DEPR:
Over 150 kg of dry single cell protein was produced and was subjected to microbiological quality
control analyses, chemical analyses, nutritional evaluation and sub-chronic toxicological
testing. The microbiological quality control tests at no time showed the presence of any
pathogenic microorganisms, and the single cell protein produced met the international standard
for microbiological testing. The results of the chemical analysis of the single cell protein
produced by Methylophilus KISRI 5 (NCIB 12135) and Methylophilus KISRI 6.1 (NCIB 12136) are shown
in Table 5. The single cell protein was tested for subchronic oral toxicity for 13 weeks in rats
by the well-known, highly-reputed International Toxicological Institute (TNO, P.O. Box 360,
Zeist, The Netherlands). The results of this study showed that the feeding of the single cell
protein produced by both KISRI 5 (NCIB 12135) and KISRI 6.1 (NCIB 12136) to rats at levels up to
30% of their total diet failed to induce any obvious deleterious effects.

40. Document ID: US 4980067 A

L10: Entry 40 of 42

File: USPT

Dec 25, 1990

US-PAT-NO: 4980067
DOCUMENT-IDENTIFIER: US 4980067 A
TITLE: Polyionene-transformed microporous membrane
DATE-ISSUED: December 25, 1990

US-CL-CURRENT: 210/638; 210/490, 427/245

DISCLAIMER DATE: 20051213
APPL-NO: 7/ 276831
DATE FILED: November 28, 1988

PARENT-CASE:
This application is a continuation-in-part application to copending application U.S. Ser. No.
758,064 filed on July 23, 1985, to be issued on Dec. 14, 1988 as U.S. Pat. No. 4,791,063 entitled
"Polyionene-Transformed Modified Polysaccharide Supports". This application is identical to U.S.
Ser. No. 758,036 filed July 23, 1985 entitled "Polyionene-Transformed Microporous Membrane", now
abandoned. The entire disclosures of these applications are incorporated herein by reference.

IN: Hou; Kenneth C., Hou; Chung-Jen, Chen; Haunn-Lin

AB: A microporous membrane modified by coating or grafting thereon a polyionene
material. The thus-modified microporous membrane is useful for separating
microorganism-originated contaminants from biological liquids.

L10: Entry 40 of 42

File: USPT

Dec 25, 1990

DOCUMENT-IDENTIFIER: US 4980067 A
TITLE: Polyionene-transformed microporous membrane

BSPR:
Rembaum, U.S. Pat. No. 4,046,750, discloses ionene modified beads for use in binding small and
large anionic compounds. The bead substrates are formed by the aqueous copolymerization of a
substituted acrylic monomer and a cross-linking agent. The formed polymeric beads are reacted
with a mixture of a ditertiary amine and a dihalide or with a dimethylaminoalkyl halide to attach
ionene segments to the halo or tertiary amine centers on the beads. The thus-formed
polyionene-modified beads find use in affinity or pellicular chromatography for removal of
heparin from its mixture with polycations or neutral substances such as proteins or serums.
Further disclosed utilities include use of the modified beads in the separation of cholesterol
precursors such as bile acid from bile micellar suspensions, for binding RNA or DNA irreversibly,
and a variety of other utilities which depend upon the binding characteristics of the
polycationic nature of the polyionene.

BSPR:
By the term "biological liquids" is meant to include each and every liquid system which is
derived from or amenable to use with living organisms. Such liquids are ordinarily handled and
processed under sanitary or sterile conditions and therefore require sanitized or sterilized
media for filtration. Included within such terms are isotonic solutions for intramuscular or
intravenous administration, solutions designated for oral administration, solutions for topical
use, biological wastes or other biological fluids which may comprise filterable bodies such as
impurities, e.g. bacteria, viruses, or endotoxins which are desirably isolated or separated for
examination or disposable by immobilization or fixation upon or entrapment within separation
media.

41. Document ID: US 4791063 A

L10: Entry 41 of 42

File: USPT

Dec 13, 1988

US-PAT-NO: 4791063
DOCUMENT-IDENTIFIER: US 4791063 A
TITLE: Polyionene transformed modified polysaccharide supports
DATE-ISSUED: December 13, 1988

US-CL-CURRENT: 435/243; 435/252.1, 435/308.1, 435/803, 524/27, 524/58, 525/54.3, 526/238.2

APPL-NO: 6/ 758064
DATE FILED: July 23, 1985

PARENT-CASE:
CROSS REFERENCE TO RELATED APPLICATIONS The present application is a continuation-in-part of
application Ser. No. 576,448, filed Feb. 2, 1984 now U.S. Pat. No. 4,663,163, which in turn is a
continuation-in-part of application Ser. No. 466,114, filed Feb. 14, 1983 now abandoned. Further,
the application is related to application Ser. No. 723,691, filed Apr. 16, 1985 now U.S. Pat. No.
4,675,104, (which is a continuation-in-part of Ser. No. 633,904, filed Jan. 23, 1985, abandoned,
which is a continuation of Ser. No. 505,532, filed June 17, 1983, now U.S. Pat. No. 4,496,461)
and application Ser. No. 758,036, filed concurrently herewith. These patent applications are
incorporated by reference herein.

IN: Hou; Kenneth C., Hou; Chung-Jen, Chen; Haunn-Lin

AB: Polyionene-transformed modified polymer-polysaccharide separation matrix and use
thereof in removing contaminants of microorganism origin from biological liquids are
disclosed.

L10: Entry 41 of 42

File: USPT

Dec 13, 1988

DOCUMENT-IDENTIFIER: US 4791063 A
TITLE: Polyionene transformed modified polysaccharide supports

BSPR:
Rembaum, U.S. Pat. No. 4,046,750, discloses ionene modified beads for use in binding small and
large anionic compounds. The bead substrates are formed by the aqueous copolymerization of a
substituted acrylic monomer and a cross-linking agent. The formed polymeric beads are reacted
with a mixture of a ditertiary amine and a dihalide or with a dimethylaminoalkyl halide to attach
ionene segments to the halo or tertiary amine centers on the beads. The thus-formed
polyionene-modified beads find use in affinity or pellicular chromatography for removal of
heparin from its mixture with polycations or neutral substances such as proteins or serums.
Further disclosed utilities include use of the modified beads in the separation of cholesterol
precursors such as bile acid from bile micellar suspensions, for binding

RNA or DNA irreversibly,
and a variety of other utilities which depend upon the binding characteristics of the
polycationic nature of the polyionene.

DEPR:
By the term "biological liquids" is meant to include each and every liquid system which is
derived from or amenable to use with living organisms. Such liquids are ordinarily handled and
processed under sanitary or sterile conditions and therefore require sanitized or sterilized
media for separation. Included within such terms are isotonic solutions for intramuscular or
intravenous administration, solutions designated for oral adminstration, solutions for topical
use, biological wastes or other biological fluids which may comprise filterable bodies such as
impurities, e.g. bacteria, viruses, or endotoxins which are desirably isolated or separated for
examination or disposable by immobilization or fixation upon or entrapment within separation
media.

42. Document ID: JP 10004918 A

L10: Entry 42 of 42
File: DWPI
Jan 13, 1998

DERWENT-ACC-NO: 1998-123754
DERWENT-WEEK: 199812

TITLE: Nutrient compositions containing nucleic acid related compounds, used for growth and
health maintenance - contain e.g. docosahexaenoic acid, arachidonic acid and cholesterol

PRIORITY-DATA: 1996JP-0177226 (June 19, 1996)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
JP 10004918 A	January 13, 1998	N/A	009	A23L001/30

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
JP10004918A	June 19, 1996	1996JP-0177226	N/A

INT-CL (IPC): A23C 9/152; A23D 9/007; A23L 1/30; A23L 1/305; C07H 21/00
IN: No data.

AB: Nutrient compositions containing nucleic acids, docosahexaenoic acid (DHA),
arachidonic acid and cholesterol for improvement of contents of lipids, proteins,
cholesterol and/or nucleic acids in biomembrane. Also claimed are (1) nucleic acids of
one or more bases composing nucleotides, nucleosides, nucleic acids (DNA, RNA) or
their components; (2) nutrient compositions contain 5-10 mg of cytidine-monophosphate,
2-4 mg of uridine-monophosphate, 0-4 mg of adenosine-monophosphate, 1-3 mg of
guanosine-monophosphate, and/or 2-4 mg of inosine-monophosphate, and 4.9-60 mg of
arachidonic acid, 24.5-250 mg of DHA and 56-90 mg of cholesterol, particularly in
edible fat, esp. including fish oil, in 100 g of powdery compositions, (3) the lipids
of fatty acids and/or glycerophospholipids, (4) the fatty acids of mono- and/or
poly-unsaturated fatty acids and glycerophosph olipids of choline containing
phospholipids, phosphatidyl choline (PC) and/or phosphatidyl ethanolamine (PE), (5)
the effective components in pure or crude form and/or those containing them, and (6)
the compositions used for human, particularly for infants, esp. modified milk, and/or
animals in medicinal and/or food or drink compositions., USE - The compositions are
for favourable growth and maintenance of healthy conditions. Administration is oral.,
ADVANTAGE - Compositions are particularly for infants in weaning stage.

L10: Entry 42 of 42
File: DWPI
Jan 13, 1998

DERWENT-ACC-NO: 1998-123754
DERWENT-WEEK: 199812
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TITLE: Nutrient compositions containing nucleic acid related compounds, used for growth and
health maintenance - contain e.g. docosahexaenoic acid, arachidonic acid and cholesterol

ABTX:
Nutrient compositions containing nucleic acids, docosahexaenoic acid (DHA), arachidonic
acid and cholesterol for improvement of contents of lipids, proteins, cholesterol and/or
nucleic acids in biomembrane. Also claimed are (1) nucleic acids of one or more bases
composing nucleotides, nucleosides, nucleic acids (DNA, RNA) or their components; (2)
nutrient compositions contain 5-10 mg of cytidine-monophosphate, 2-4 mg of
uridine-monophosphate, 0-4 mg of adenosine-monophosphate, 1-3 mg of
guanosine-monophosphate, and/or 2-4 mg of inosine-monophosphate, and 4.9-60 mg of
arachidonic acid, 24.5-250 mg of DHA and 56-90 mg of cholesterol, particularly in edible
fat, esp. including fish oil, in 100 g of powdery compositions, (3) the lipids of fatty
acids and/or glycerophospholipids, (4) the fatty acids of mono- and/or poly-unsaturated
fatty acids and glycerophosph olipids of choline containing phospholipids, phosphatidyl
choline (PC) and/or phosphatidyl ethanolamine (PE), (5) the effective components in pure or
crude form and/or those containing them, and (6) the compositions used for human,
particularly for infants, esp. modified milk, and/or animals in medicinal and/or food or
drink compositions.

ABTX:

USE - The compositions are for favourable growth and maintenance of healthy conditions.

Administration is oral.